Determining reaction mechanisms

41

Connections

Building on:

- Mainly builds on ch13
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- Nucleophilic substitution at saturated carbon ch17
- Controlling stereochemistry ch16, ch33, & ch34
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Arriving at:

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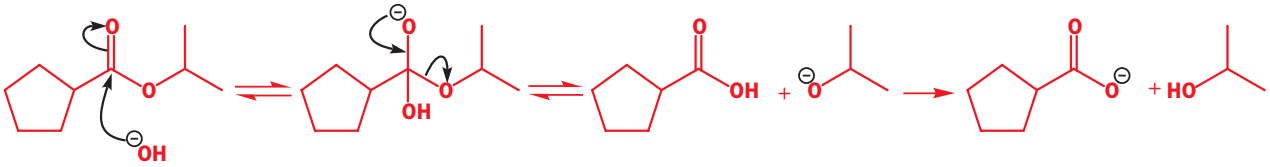
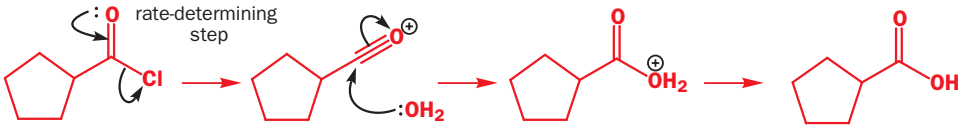
There are mechanisms and there are mechanisms

If you were asked to draw the mechanism of an ester hydrolysis in basic solution you should have no trouble in giving a good answer. It wouldn't matter if you had never seen this particular ester before or even if you knew that it had never actually been made, because you would recognize that the reaction belonged to a class of well known reactions (carbonyl substitution reactions, Chapter 12) and you would assume that the mechanism was the same as that for other ester hydrolyses. And you would be right—nucleophilic attack on the carbonyl group to form a tetrahedral intermediate is followed by loss of the alkoxide leaving group and the formation of the anion of the carboxylic acid.



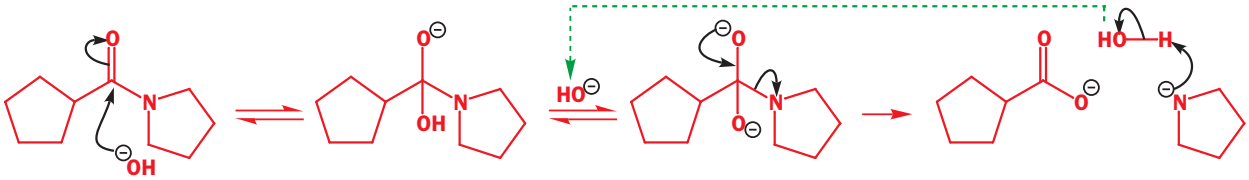
But someone at some time had to determine this mechanism in full detail. That work was done in the 1940s to 1960s and it was done so well that nobody seriously challenges it. You might also recall from Chapter 13 that, if we change the carbonyl compound to an acid chloride, the mechanism may change to an S_N1 type of reaction with an acylium ion intermediate because the leaving group is now much better: Cl^- is more stable (less basic) than RO^-. It would not be worth using hydroxide for this reaction: as the first step is the slow step, water will do just as well. Again someone had to determine this mechanism, had to show which was the slow step, and had to show that leaving group ability depended on pK_{aH}.

■ The link between leaving group ability and pK_{aH} was discussed in Chapter 12.



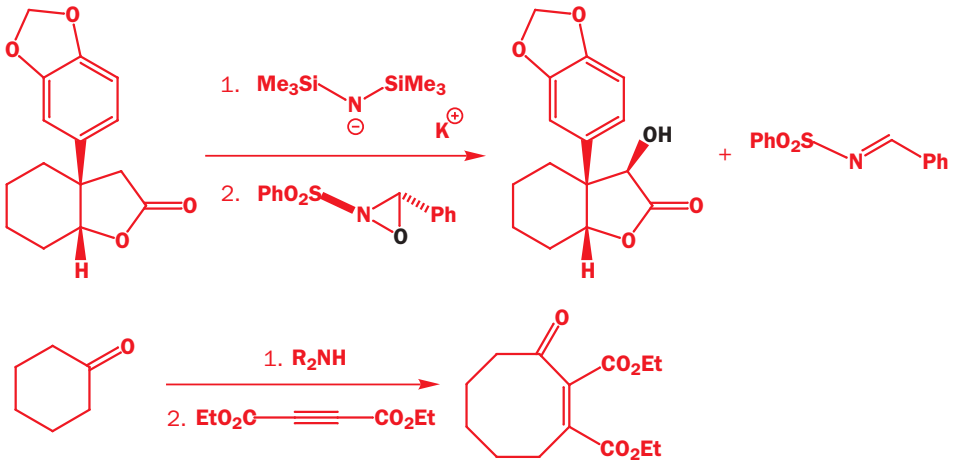
If the reaction were the hydrolysis of an amide, you might remember from Chapter 13 that third-order kinetics are often observed for the expulsion of such bad leaving groups and that this extra catalysis makes it worthwhile using concentrated base. Again, someone had to find out that: (1) the slow step is now the decomposition of the tetrahedral intermediate; (2) there are third-order kinetics involving two molecules of hydroxide; and (3) the first molecule acts as a nucleophile and the second as a base.

■ This chemistry was discussed in Chapter 13.



These reactions are versions of the same reaction. For you, writing these mechanisms chiefly means recognizing the type of reaction (nucleophilic substitution at the carbonyl group) and evaluating how good the leaving group is. For the original chemists, determining these reaction mechanisms meant: (1) determining exactly what the product is (that may sound silly, but it is a serious point); (2) discovering how many steps there are and the structures of the intermediates; (3) finding out which is the slow (rate-determining) step; and (4) finding any catalysis. This chapter describes the methods used in this kind of work.

Supposing you were asked what the mechanisms of the next two reactions might be. This is a rather different sort of problem as you probably don't recognize any of these reagents and you probably cannot fit any of the reactions into one of the classes you have seen so far. You probably don't even see at once which of the three main classes of mechanism you should use: ionic; pericyclic; or radical.



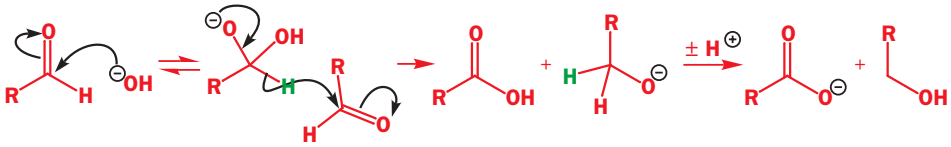
There are two types of answer to the question: 'What is the mechanism of this reaction?' You may do your best to write a mechanism based on your understanding of organic chemistry, moving the electrons from nucleophiles to electrophiles, choosing sensible intermediates, and arriving at the right products. You would not claim any authority for the result, but you would hope, as an organic chemist, to produce one or more reasonable mechanisms. This process is actually an essential preliminary to answering the question in the second way—'What is the real, experimentally verified, mechanism for the reaction?' This chapter is about the second kind of answer.

Determining reaction mechanisms—the Cannizzaro reaction

So how do we know the mechanism of a reaction? The simple answer is that we don't for certain. Organic chemists have to face situations where the structure of a compound is initially thought to be one thing but later corrected to be something different. The same is true of mechanisms. It is the nature of science that all we can do is try to account for observations by proposing theories. We then test the theory by experiment and, when the experiment does not fit the theory, we must start again with a new theory. This is exactly the case with mechanisms. When a new reaction is discovered, one or more mechanisms are proposed; evidence is then sought for and against these mechanisms until one emerges as the best choice and that remains the accepted mechanism for the reaction until fresh evidence comes along that does not fit the mechanism.

We are going to look at one reaction, the Cannizzaro reaction, and use this to introduce the different techniques used in elucidating mechanisms so that you will be able to appreciate the different information each experiment brings to light and how all the pieces fit together to leave us with a probable mechanism. Under strongly basic conditions, an aldehyde with no α hydrogens undergoes disproportionation to give half alcohol and half carboxylate. Disproportionation means one half of the sample is oxidized by the other half, which is itself reduced. In this case, half the aldehyde reduces the other half to the primary alcohol and in the process is oxidized to the carboxylic acid. Before the discovery of $LiAlH_4$ in 1946, this was one of the few reliable ways to reduce aldehydes and so was of some use in synthesis.

■ The Cannizzaro reaction first appeared in Chapter 27.



The mechanism we have drawn here is slightly different from that in Chapter 27 where we showed the dianion as an intermediate. The two reactions are related by base catalysis as we shall see. Now for some of the evidence and some of the alternative mechanisms that have been proposed for the Cannizzaro reaction. Most of these have been eliminated, leaving just the ones you have already met. Finally, we will see that even these mechanisms do not explain everything absolutely.

Proposed mechanism A—a radical mechanism

Early on it was thought that the hydrogen transfer might be taking place via a radical chain reaction. If this were the case, then the reaction should go faster if radical initiators are added and it should slow down when radical inhibitors are added. When this was tried, there was no change in the rate, so this proposed mechanism was ruled out.

■ For some examples of radical initiators, see Chapter 39. Radical inhibitors are usually stable radicals such as those on p. 000.

Kinetic evidence for an ionic mechanism

The first piece of evidence that must be accounted for is the rate law. For the reaction of benzaldehyde with hydroxide, the reaction is first-order with respect to hydroxide ions and second-order with respect to benzaldehyde (third-order overall).

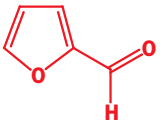
$$\text{rate} = k_3[\text{PhCHO}]^2[\text{HO}^-]$$

For some aldehydes, such as formaldehyde and furfural, the order with respect to the concentration of hydroxide varies between one and two depending on the exact conditions. In high concentrations of base it is fourth-order.

$$\text{rate} = k_4[\text{HCHO}]^2[\text{HO}^-]^2$$

At lower concentrations of base it is a mixture of both third- and fourth-order reactions.

$$\text{rate} = k_3[\text{HCHO}]^2[\text{HO}^-] + k_4[\text{HCHO}]^2[\text{HO}^-]^2$$



2-furaldehyde (furfural)

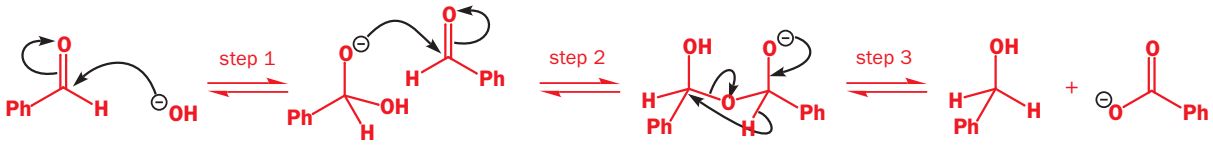
Just because the overall order of reaction is third- or fourth-order, it does not mean that all the species must simultaneously collide in the rate-determining step. You saw in Chapter 13 that the rate law actually reveals all the species that are involved *up to and including* the rate-determining step.

Isotopic labelling

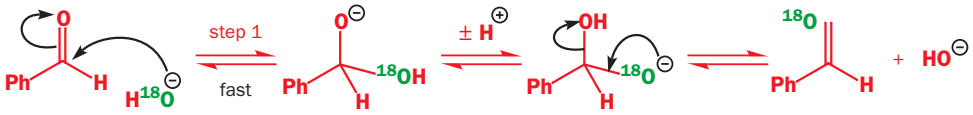
When the reaction is carried out in D_2O instead of in H_2O it is found that there is are no C–D bonds in the products. This tells us that the hydrogen must come from the aldehyde and not from the solvent.

Proposed mechanism B—formation of an intermediate dimeric adduct

A possible mechanism that fits all the experimental evidence so far involves nucleophilic attack of the usual tetrahedral intermediate on another aldehyde to give an intermediate adduct. This adduct could then form the products directly by hydride transfer. You may not like the look of this last step, but the mechanism was proposed and evidence is needed to disprove it.

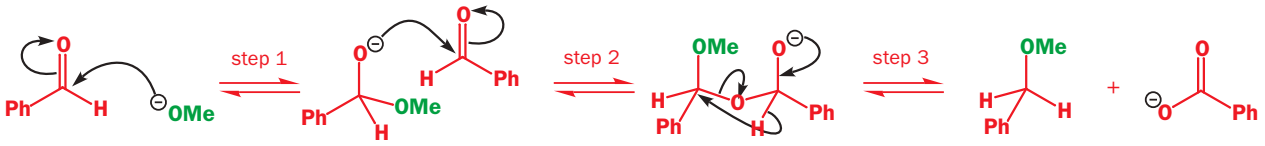


Which step would be rate-determining for this mechanism? It could not be step 1 since, if this were the case, then the rate law would be first-order with respect to the aldehyde rather than the observed second-order relationship. Also, if the reaction is carried out in water labelled with oxygen-18, the oxygen in the benzaldehyde exchanges with the ^{18}O from the solvent much faster than the Cannizzaro reaction takes place. This can only be because of a *rapid* equilibrium in step 1 and so step 1 cannot be rate-determining.



So, for mechanism B, either step 2 or step 3 could be rate-determining—either case would fit the observed rate law. Step 2 is similar to step 1; in both cases an oxyanion nucleophile attacks the aldehyde. Since the equilibrium in step 1 is very rapid, it is reasonable to suggest that the equilibrium in step 2 should also be rapid and thus that the hydride transfer in step 3 must be rate-determining. So mechanism B can fit the rate equation.

How can mechanism B be ruled out? One way is to change the attacking nucleophile. The Cannizzaro reaction works equally well if methoxide is used in a mixture of methanol and water. If mechanism B were correct, the reaction with methoxide would be as follows.



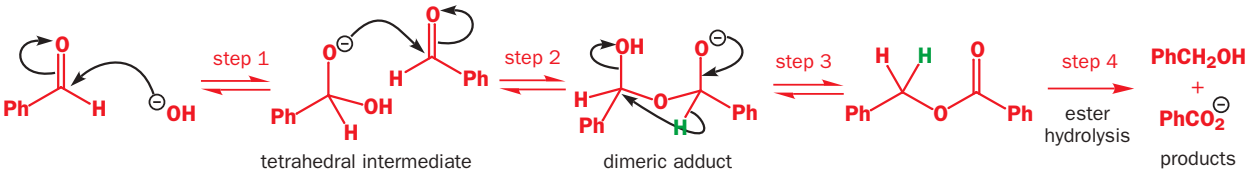
■ We shall discuss this kind of technique as well as other evidence used to evaluate an intermediate towards the end of this chapter.

One of the products would be different by this mechanism: benzyl methyl ether would be formed instead of benzyl alcohol. None is observed experimentally. Under the conditions of the experiment, benzyl methyl ether does not react to form benzyl alcohol, so it cannot be the case that the ether is formed but then reacts to form the products. Mechanism B can therefore be ruled out.

Proposed mechanism C—formation of an ester intermediate

This mechanism is like mechanism B but the hydride transfer in the adduct formed in step 2 displaces OH^- to form an ester (benzyl benzoate) that is then hydrolysed to the products. This was at

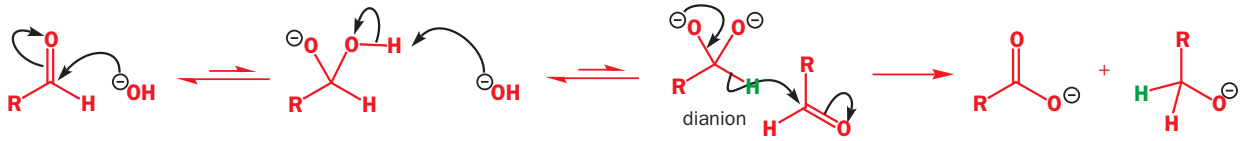
one time held to be the correct mechanism for the Cannizzaro reaction. One piece of evidence for this, and at first glance a very good one, is that by cooling the reaction mixture and avoiding excess alkali, some benzyl benzoate could be isolated during the reaction. An important point is that this does not mean that the ester *must* be an intermediate in the reaction—it might be formed at the end of the reaction, for example. However, it does mean that any mechanism we propose must be able to account for its formation. For now though we want to try and establish whether the ester is an *intermediate* rather than a by-product in the Cannizzaro reaction.



An early objection to mechanism C was that the ester would not be hydrolysed fast enough. When someone actually tried it under the conditions of the experiment, they found that benzyl benzoate is very rapidly hydrolysed (the moral here is 'don't just think about it, try it!'). However, just because the ester *could* be hydrolysed, it still did not show that it actually was an intermediate in the reaction. How this was eventually shown was rather clever. The argument goes like this. We can measure the rate constant for step 4 by seeing how quickly pure benzyl benzoate is hydrolysed to benzyl alcohol and benzoate under the same conditions as those of the Cannizzaro reaction. We also know how quickly these products are formed during the Cannizzaro reaction itself. Since, if this mechanism is correct, the only way the products are formed is from this intermediate, it is possible to work out how much of the intermediate ester must be present at any time to give the observed rate of formation of the products. If we can measure the amount of ester that is actually present and it is significantly less than that which we predict, then this cannot be the correct mechanism. It turned out that there was never enough ester present to account for the formation of the products in the Cannizzaro reaction and mechanism C could be ruled out.

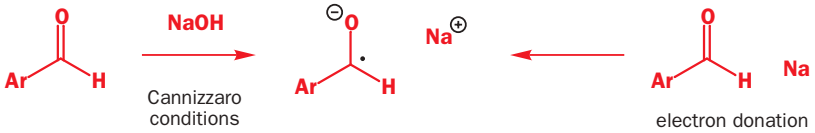
The correct mechanism for the Cannizzaro reaction

The only mechanism that has not been ruled out and that appears to fit all the evidence is the one we have already given (p. 000). The fact that the rate law for this mechanism is overall third- and sometimes fourth-order depending on the aldehyde and the conditions can be explained by the involvement of a second hydroxide ion deprotonating the tetrahedral intermediate to give a dianion. When methoxide is used in a methanol/water mix, some methyl ester is formed. This does not stay around for long—under the conditions of the experiment it is quickly hydrolysed to the carboxylate.



Even this mechanism does not quite fit all the evidence

We said earlier that we can never prove a mechanism—only disprove it. Unfortunately, just as the 'correct' mechanism seems to be found, there are some observations that make us doubt this mechanism. In Chapter 39 you saw how a technique called **electron spin resonance** (ESR) detects radicals and gives some information about their structure. When the Cannizzaro reaction was carried out with benzaldehyde and a number of substituted benzaldehydes in an ESR spectrometer, a radical was detected. For each aldehyde used, the ESR spectrum proved to be identical to that formed when the aldehyde was reduced using sodium metal. The radical formed was the radical anion of the aldehyde.



Our mechanism does not explain this result but small amounts of radicals are formed in many reactions in which the products are actually formed by simple ionic processes. Detection of a species in a reaction mixture does not prove that it is an intermediate. Only a few chemists believe that radicals are involved in the Cannizzaro reaction. Most believe the mechanism we have given.

Variation in the structure of the aldehyde

Before leaving the Cannizzaro reaction, look at these rates of reactions for aromatic aldehydes with different substituents in the *para* position. These aldehydes may be divided into two classes: those that react faster than unsubstituted benzaldehyde and those that react more slowly. Those that go slower all have something in common—they all have substituents on the ring that donate electrons.

Aldehyde	Rate relative to benzaldehyde at 25 °C	Rate relative to benzaldehyde at 100 °C
benzaldehyde	1	1
p-methylbenzaldehyde	0.2	0.2
p-methoxybenzaldehyde	0.05	0.1
p-dimethylaminobenzaldehyde	very slow	0.0004
p-nitrobenzaldehyde	210	2200

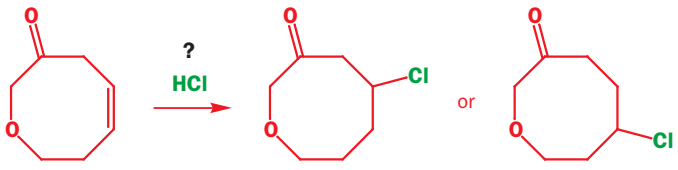
We have already seen how substituents on a benzene ring affect the rate of electrophilic substitution (Chapter 22). Electron-donating groups such as MeO– and Me_2N– dramatically speed up the rate at which an aromatic ring is attacked by an electrophile, whereas electron-withdrawing groups, particularly nitro groups, slow the reaction down. The Cannizzaro reaction is not taking place on the benzene ring itself, but substituents on the ring still make their presence known. The fact that the Cannizzaro reaction goes much *slower* with electron-donating groups and faster with electron-withdrawing groups tells us that, for this reaction, rather than a positive charge developing as in the case of electrophilic substitution on an aromatic ring, there must be negative charge accumulating somewhere near the ring. Our mechanism has mono- and dianion intermediates that are stabilized by electron-withdrawing groups. Later in the chapter you will see a more quantitative treatment of this variation of structure.

The rest of the chapter is devoted to discussions of the methods we have briefly surveyed for the Cannizzaro reaction with examples of the use of each method. We give examples of many different types of reaction but we cannot give every type. You may rest assured that all of the mechanisms we have so far discussed in this book have been verified (not, of course, proved) by these sorts of methods.

Be sure of the structure of the product

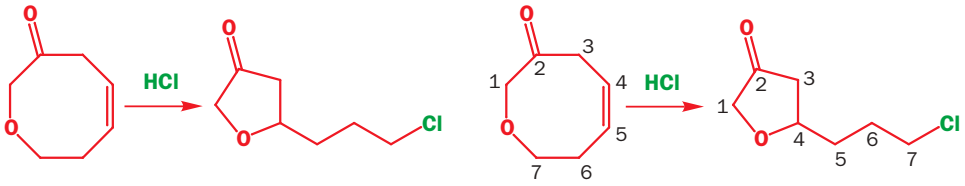
This seems a rather obvious point. However, there is a lot to be learned from the detailed structure of the product and we will discuss checking which atom goes where as well as the stereochemistry of the product. You will discover that it may be necessary to alter the structure of the starting material in subtle ways to make sure that we know exactly what happens to all its atoms by the time it reaches the product.

Suppose you are studying the addition of HCl to this alkene. You find that you get a good yield of a single adduct and you might be a bit surprised that you do not get a mixture of the two obvious adducts and wonder if there is some participation of the ether oxygen or whether perhaps the ketone enolizes during the reaction and controls the outcome.

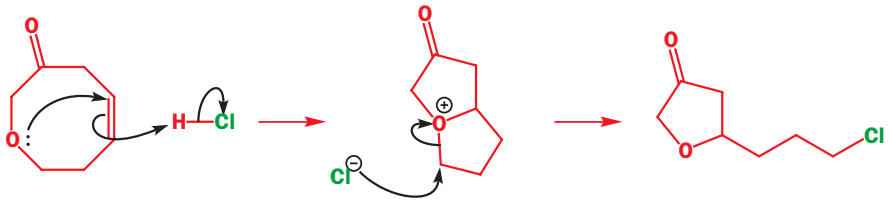


If you are cautious you might check on the structure of the product before you start a mechanistic investigation. The NMR spectrum tells you at once that the product is neither of these suggestions. It contains a $(CH_2)_3Cl$ unit and can no longer have an eight-membered ring. A ring

contraction has given a five-membered ring and a mechanistic investigation is hardly needed. Simply knowing what the product is allows us to propose a mechanism. A rearrangement has occurred and we could use the method suggested in Chapter 37, of numbering the atoms in the starting material and finding them in the product. This is quite easy as only one numbering system makes any sense.



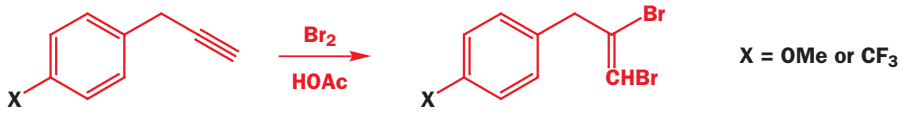
This numbering suggests that the carbon skeleton is unaffected by the reaction, that protonation has occurred at C5, that the ether oxygen has acted as an internal nucleophile across the ring at C4, and that the chloride ion has attacked C7. The mechanism is straightforward.



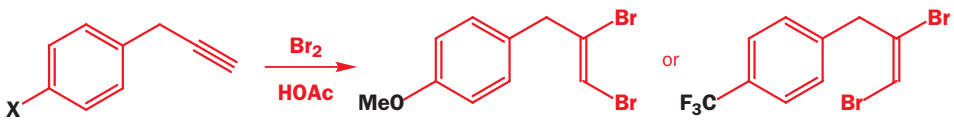
It may be disappointing to find that every step in this mechanism is well known and that the reaction is exactly what we ought to have expected with an eight-membered ring as these rings are famous for their transannular (across-ring) reactions to form 5/5 fused systems. However, it is good that a prolonged investigation is not necessary.

> **Find out for sure what the structure of the product is before you start a mechanistic investigation.**

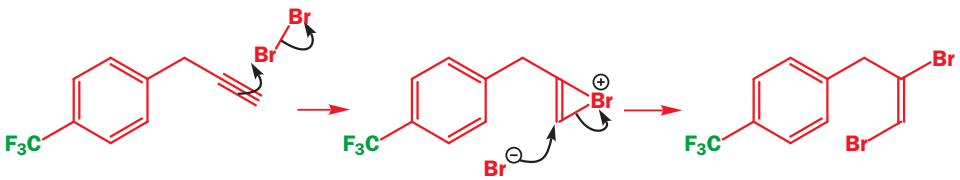
A more subtle distinction occurred in a study of the bromination of alkynes. Bromination of benzyl alkynes in acetic acid gave the products of addition of one molecule of bromine—the 1,2-dibromoalkenes. The reaction was successful with a variety of *para* substituents and there seems at first to be no special interest in the structure of the products.



Closer investigation revealed an extraordinary difference between them, not at all obvious from their NMR spectra: the compound from X = OMe was the *Z*-dibromoalkene from *cis* addition of bromine while the product from X = CF_3 was the *E*-alkene from *trans* addition. What mechanism could explain this difference?

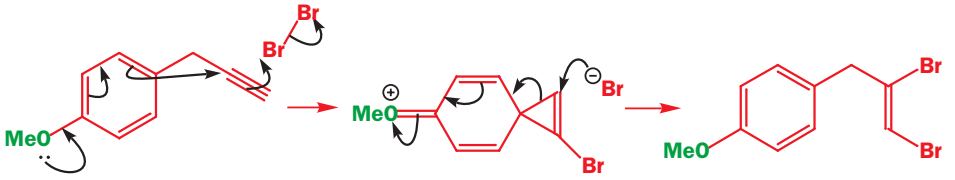


The *anti* addition is more easily explained: it is the result of formation of a bromonium ion, similar, in fact, to the normal mechanism for the bromination of alkenes. Bromine adds from one side of the alkene and the bromide ion must necessarily form the *E*-dibromo product regardless of which atom it attacks.



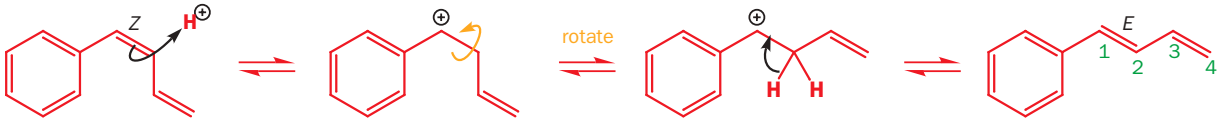
So why does the *p*-MeO– compound behave differently? It cannot react by the same mechanism and a reasonable explanation is that the much more electron-donating ring participates in the reaction to give a carbocyclic three-membered ring intermediate that is attacked in an *anti* fashion to give the *Z*-alkene. Both intermediates are three-membered ring cations and both are attacked with inversion but the *p*-MeO– compound undergoes double inversion by participation of the ring.

■ A similar aryl participation in saturated compounds to give a 'phenonium ion' intermediate appears in Chapter 37, p. 000.

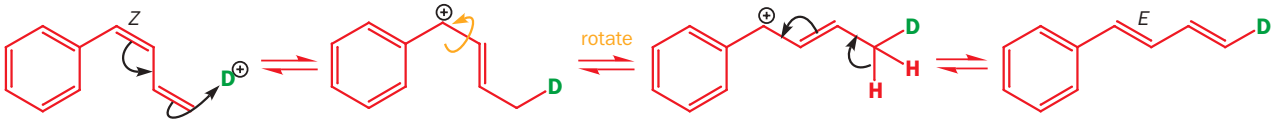


Labelling experiments reveal the fate of individual atoms

It often happens that the atoms in starting material and product cannot be correlated without some extra distinction being made by isotopic labelling. The isomerization of *Z*-1-phenylbutadiene to the *E*-diene in acid looks like a simple reaction. Protonation of the *Z*-alkene would give a stabilized secondary benzylic cation that should last long enough to rotate. Loss of the proton would then give the more stable *E*-diene.



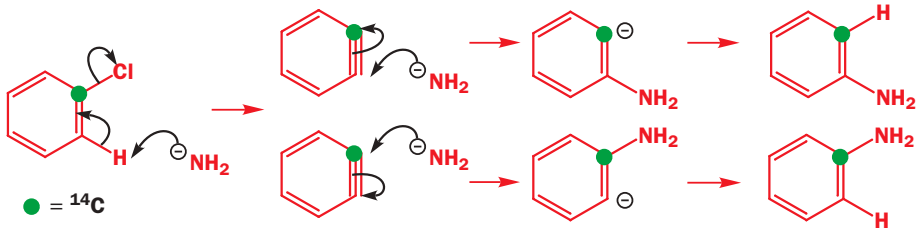
However, reaction with D^+ in D_2O reveals that this mechanism is incorrect. The product contains substantial amounts of deuterium at C4, not at C2 as predicted by the proposed mechanism. Protonation must occur at the end of the conjugated system to produce the more stable conjugated cation, which rotates about the same bond and loses H or D from C4 to give the product. More H than D will be lost, partly because there are two Hs and only one D, but also because of the kinetic isotope effect, of which more later.



▶ Tritium and ^{14}C are β emitters—they give off electrons—having half-lives of 12 and over 5000 years, respectively. Tritium is made on a large scale by neutron irradiation of ^{6}Li in a nuclear reactor.

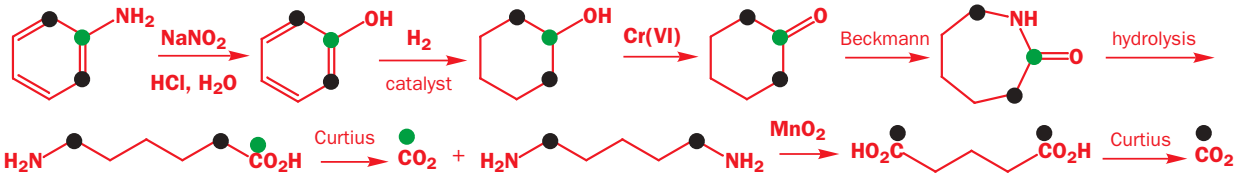
The easiest labels to use for this job are D for H, ^{13}C, and ^{18}O. None of these is radioactive; all can be found by mass spectrometry, while D and ^{13}C can be found by NMR. Old work on mechanisms used radioactive tracers such as T (tritium) for H and ^{14}C. These are isotopes of hydrogen and carbon having extra neutrons. They are, of course, more dangerous to use but they can at least always be found. The real disadvantage is that, to discover exactly where they are in the product, the molecule must be degraded in a known fashion. These radioactive isotopes are not much used nowadays except in determining biological mechanisms as you will see in Chapters 49–51. The first evidence for benzyne as the intermediate in the reaction of chlorobenzene with NH_2^- came from radioactive labelling.

■ Benzyne is discussed in Chapter 23 as an intermediate in nucleophilic aromatic substitution.



benzyne

If benzyne is an intermediate, the product should have 50% label at C1 and 50% at the two identical *ortho* carbons. The labelled aniline was degraded by the reactions shown here, which you must agree was a lot of work for the chemists concerned. Each potentially labelled carbon atom had to be isolated from any other labelled atom and the radioactivity measured. We shall follow the fate of the two labelled atoms with black and green spots. Since the two *ortho* positions are identical, we must put a green spot on both of them.

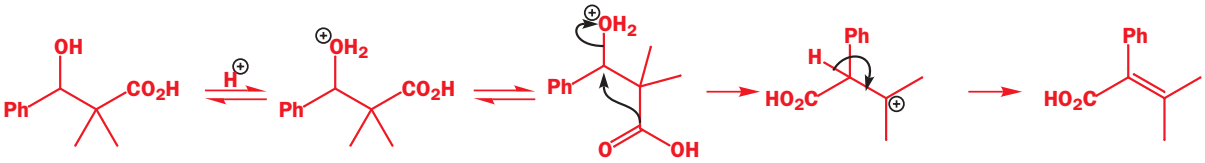


Most of these reactions are well known—the Beckmann rearrangement is described in Chapter 37 and the Curtius reaction in Chapter 40—but the oxidation of the diamine to the dicarboxylic acid is not a standard procedure and is not recommended. All the label came out in the CO_2 and almost exactly half of it was from the black and half from the green labelled carbons. This was the original evidence that convinced organic chemists in 1953 that benzyne was involved in the reaction. The evidence presented in Chapter 23 is more modern.

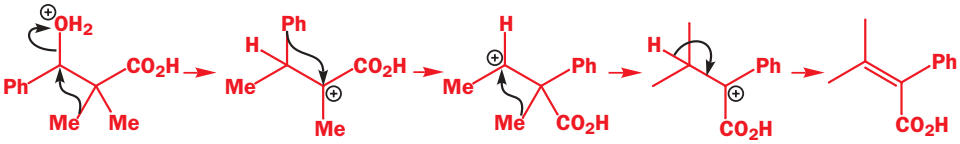
■ Other symmetrical intermediates originally identified by radioactive labelling include the cyclopropanone in the Favorskii rearrangement in Chapter 37, p. 000, and a spirocyclic intermediate in electrophilic substitution on an indole in Chapter 43, p. 000.

The value of double labelling experiments

An altogether more modern approach to a labelling study was used in the surprising rearrangement of a hydroxy-acid in acidic solution. The structure of the product suggests a CO_2H migration as the most likely mechanism. This mechanism resembles closely the cationic rearrangements of Chapter 37.

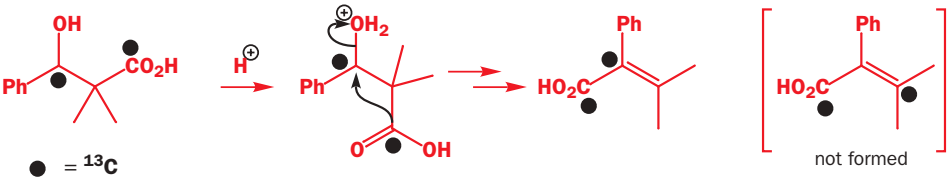


Received wisdom (Chapter 37) objects that the best migrating group in cationic rearrangements is the one best able to bear a positive charge, so that the more familiar Ph and Me migrations ought to be preferred and that a more elaborate mechanism should be sought. Such a mechanism can be written: it involves two methyl migrations and one phenyl migration and is acceptable.



These mechanisms can be tested by finding out whether the CO_2H group remains attached to its original position or becomes attached to the other carbon in the skeleton of the molecule. This can be done by double labelling. If a compound is prepared with two ^{13}C labels, one on the CO_2H group itself and one on the benzylic carbon, the NMR spectrum of the product will show what has happened. In fact, the two ^{13}C labels end up next to each other with a coupling constant $^1J_{CC} = 71$ Hz. It is the CO_2H group that has migrated.

■ This style of double labelling with NMR active isotopes will be seen again in Chapters 49–51.

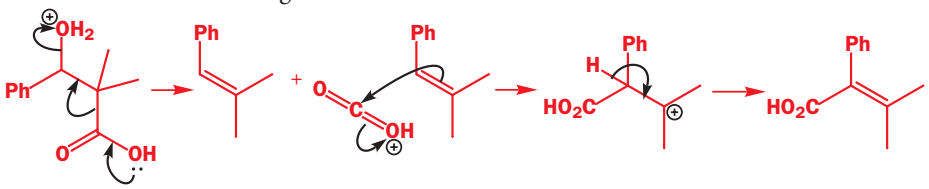


So why does the CO_2H group migrate? It does so not because it is a good migrating group but because it cannot bear to be left behind. The rearranged cation from CO_2H migration is a stable tertiary alkyl cation. The cation from Me migration is a very unstable cation with the positive charge

next to the CO_2H group. Such cations are unknown as the carbonyl group is very electron-withdrawing. Received wisdom needs to be amended.

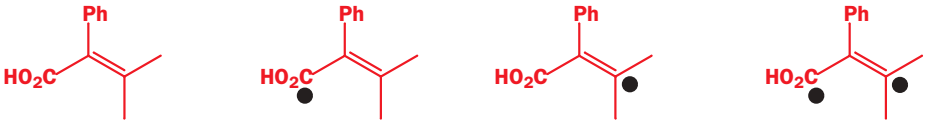
'Crossover' experiments

There is still one tiny doubt. Supposing the reaction is not intramolecular at all, but intermolecular. The CO_2H group might be lost from one molecule as protonated CO_2 and be picked up by another molecule of alkene. No migration would be involved at all.



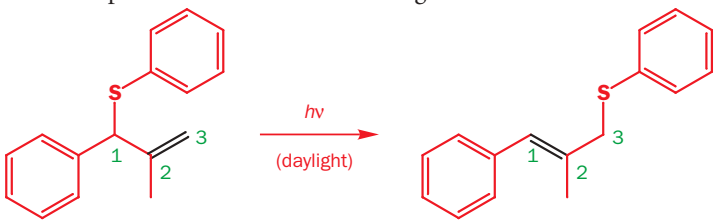
This mechanism can be checked by using a 50:50 mixture of doubly labelled and unlabelled starting material. The molecule of alkene that captures the roving protonated labelled CO_2 might happen to be labelled too but equally well it might be unlabelled. If this last mechanism is correct, we should get a mixture of unlabelled, singly labelled, and doubly labelled product in the ratio 1:2:1 as there are two types of singly labelled product. The two singly labelled compounds are called the **crossover products** and the experiment is called a **crossover experiment** as it discovers whether any parts of one molecule cross over to another.

■ There is an example of a crossover experiment proving that an S_N2 reaction is intermolecular in Chapter 42, p. 000.



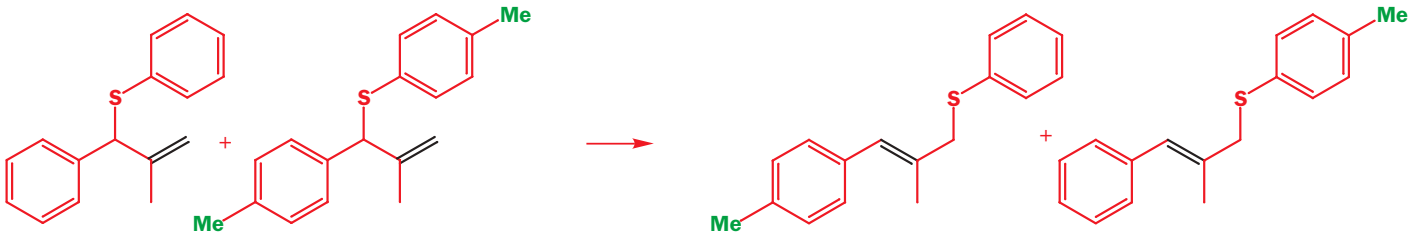
unlabelled singly labelled (two types) doubly labelled

In fact, no singly labelled compounds were found: NMR analysis showed that the product consisted entirely of unlabelled or doubly labelled molecules. The CO_2H group remains attached to the same molecule (though not to the same atom) and the first mechanism is correct. Crossover experiments demand some sort of double labelling, which does not have to be isotopic. An example where crossover products are observed is the light-initiated isomerization of allylic sulfides.



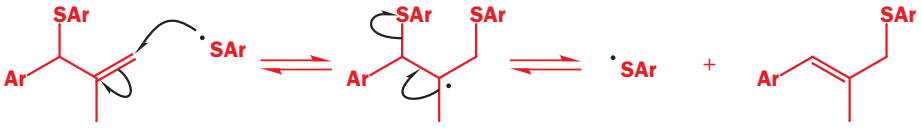
This is formally a [1,3] sigmatropic shift of sulfur (Chapter 36) but that is an unlikely mechanism and a crossover experiment was carried out in which the two molecules had either two phenyl groups or two *para*-tolyl groups.

The mixture was allowed to rearrange in daylight and the products were examined by mass spectroscopy. There was a roughly 1:2:1 mixture of products having two phenyl groups, one phenyl and one *para*-tolyl group, and two *para*-tolyl groups. The diagram shows the starting materials and the two crossover products only.



the two crossover products

Clearly, the ArS group had become separated from the rest of the molecule and the most likely explanation was a radical chain reaction (Chapter 39) with the light producing a small amount of ArS$^{\bullet}$ to initiate the chain. The *para*-methyl group acts as a label. The whole system is in equilibrium and the more highly substituted alkene is the product.

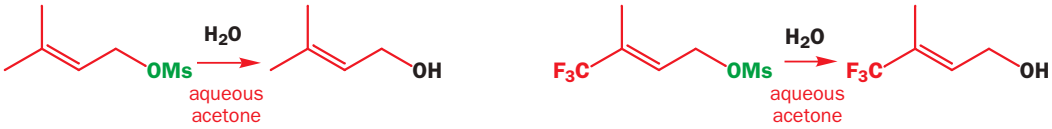


Systematic structural variation

In this last example, the hope is that the *para*-methyl group will have too weak an electronic or steric effect and in any case will be too far away to affect the outcome. It is intended to make nearly as slight a change in the structure as an isotopic label. Many structural investigations have exactly the opposite hope. Some systematic change is made in the structure of the molecule in the expectation of a predictable change in rate. A faster or slower reaction will lead to some definite conclusion about the charge distribution in the transition state.

Allylic compounds can react efficiently with nucleophiles by either the S_N1 or S_N2 mechanisms (Chapter 17) as in these two examples.

The carbon skeleton is the same in both reactions but the leaving groups and the nucleophiles are different. These reaction might both go by S_N1 or S_N2 or one might go by S_N1 and the other by S_N2. One way to find out is to make a large change in the electronic nature of the carbon skeleton and see what happens to the rate of each reaction. In these experiments one of the methyl groups was changed for a CF_3 group—exchanging a weakly electron-donating group for a strongly electron-withdrawing group. If a cation is an intermediate, as in the S_N1 reaction, the fluorinated compound will react much more slowly. Here is the result in the first case.



relative rate = 1.0

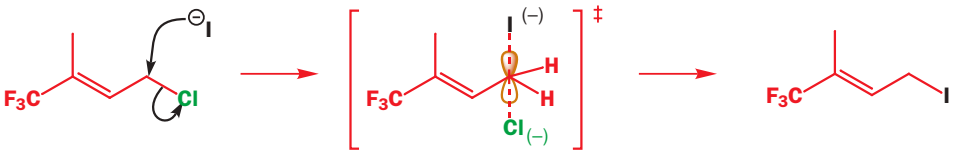
relative rate = 1.8×10^{-6}

The fluorinated compound reacts half a million times more slowly so this looks very much like an S_N1 mechanism. The slow step in an S_N1 mechanism is the formation of a carbocation so any group that destabilizes the positive charge would have (and evidently does have) a large effect on the rate. Rate ratios of several powers of ten are worth noticing and a rate ratio of nearly 10^{-6} is considerable. In the second case the rate difference is much less.

relative rate = 1.0

relative rate = 11.0

A rate ratio of 11 is not worth noticing. The point is not that the fluorinated compound reacts faster but that the two compounds react at about the same rate. This strongly suggests that no charge is generated in the transition state and an S_N1 mechanism is not possible. The S_N2 mechanism makes good sense with its concerted bond formation and bond breaking requiring no charge on the carbon skeleton.



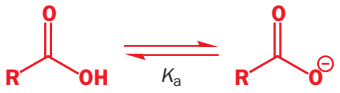
S_N2 transition state

The CF_3 group works well here as a mechanistic probe because it is held well out of the way of the reaction site by a rigid π system but is connected electronically by that same allylic system. Steric effects should be minimized and electronic effects clearly seen. This approach is clearly limited by the small number of groups having properties like those of the CF_3 group and the small number of reactions having such favourable carbon skeletons. We will now present the most important serious correlation between structure and reactivity.

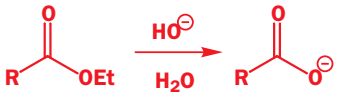
The Hammett relationship

■ Louis P. Hammett (1894–1987) invented 'physical organic chemistry' and at Columbia University in 1935 derived the Hammett σ/ρ relationship. The impact was enormous and in the 1960s chemists were still working out more such correlations.

What we would ideally like to do is find a way to quantify the effects that electron-donating or -withdrawing groups have on the transition state or intermediate during the course of a reaction. This will then give us an idea of what the transition state is really like. The first question is: can we define exactly how efficient a given group is at donating or withdrawing electrons? Hammett took the arbitrary decision to use the pK_a of an acid as a guide. For example, the rate of hydrolysis of esters might well correlate with the pK_a of the corresponding acid.

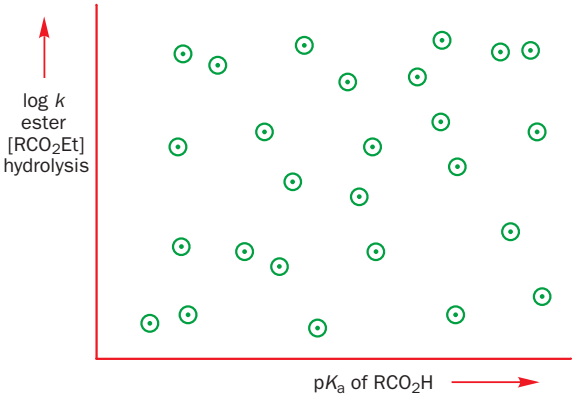


substituent on R is mechanistic probe

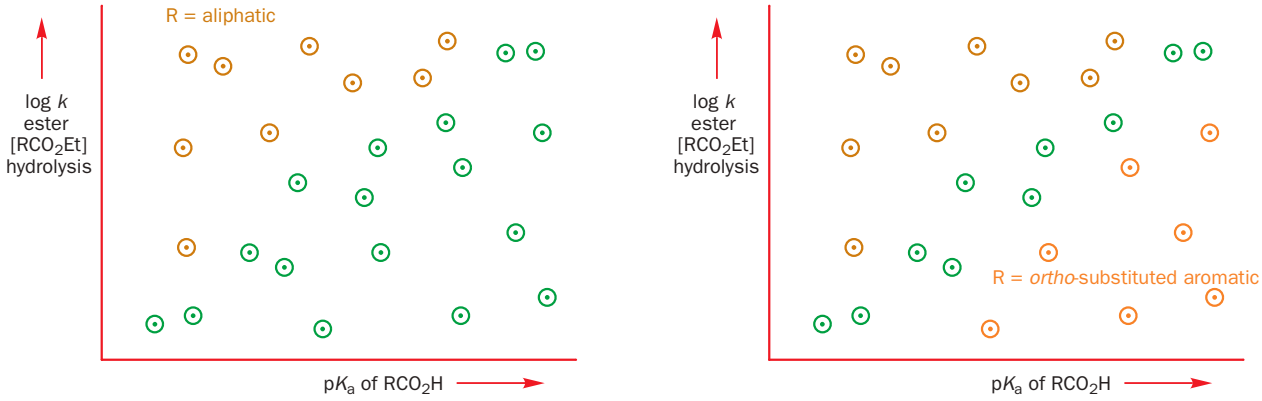


reaction to be investigated

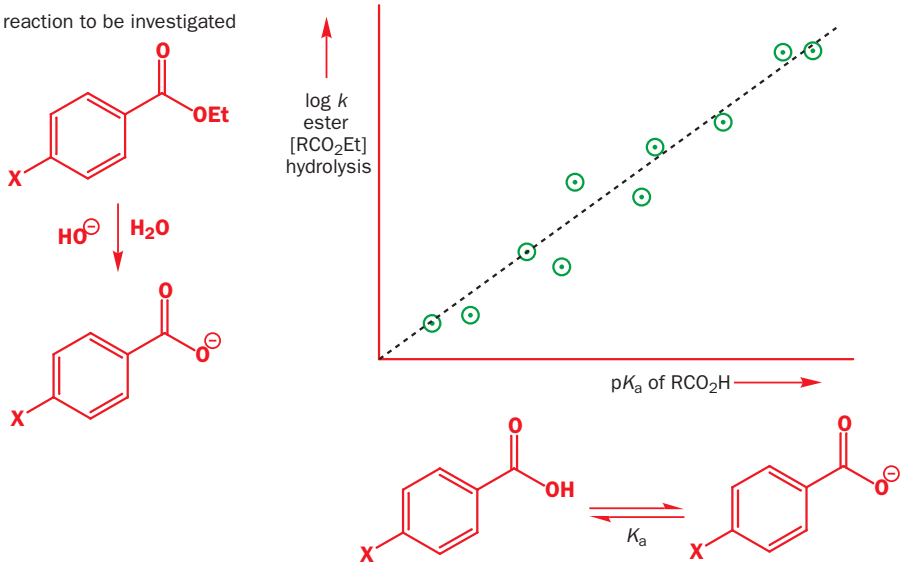
When Hammett plotted the rates of ethyl ester hydrolyses (as log k since pK_a has a log scale) against the pK_as of the corresponding acids, the initial results were not very encouraging as there was a random scatter of points over the whole graph.



Hammett had used some aliphatic acids (substituted acetic acids) and some aromatic acids (substituted benzoic acids) and he noticed that many of the points towards the top of the graph belonged to the substituted acetic acids. Removing them (brown points) made the graph a lot better. He then noticed that the remaining aromatic compounds were in two classes: the *ortho*-substituted esters reacted more slowly than their *meta*- and *para*-isomers and came towards the bottom of the graph (orange points). Removing them made the graph quite good (remaining green points).



It was not a perfect correlation but Hammett had removed the examples where steric hindrance was important. Aliphatic compounds can adopt a variety of conformations (Chapter 18) and the substituent in some of them will interfere with the reaction. Similarly, in *ortho*-substituted aromatic compounds the nearby substituent might exert steric hindrance on the reaction. Only with *meta*- and *para*-substituted compounds was the substituent held out of the way, on a rigid framework, and in electronic communication with the reaction site through the flat but conjugated benzene ring. The diagrams show the *para* substituent.



Notice that the straight line is not perfect. This graph is an invention of the human mind. It is a correlation between things that are not directly related. If you determine a rate constant by plotting the right function of concentration against time and get an imperfect straight line, that is your fault because you haven't done your measurements carefully enough. If you make a Hammett plot and the points are not on a straight line (and they won't be) then that is *not* your fault. The points really don't fit on a perfectly straight line. As you will see soon, this does not matter. We need to look at the Hammett correlation in more detail.

▶ If you plot a graph to correlate the number of miles travelled by jumbo jet against the percentage of births outside of marriage over the twentieth century you will get a sort of straight line. This does not imply a direct causative link!

The Hammett substituent constant σ

A quick glance at the pK_as of some substituted benzoic acids will show how well they correlate electron donation with pK_a. The substituents at the top of the table are electron-donating and the anions of the benzoic acids are correspondingly less stable so these are the weakest acids. At the bottom of the table we have the electron-withdrawing groups, which stabilize the anion and

▶ You cannot push arrows from the negative charge or the carboxylate into the ring. Try it.

make the acid stronger. The whole range is not that great, only one pH unit or so, because the carboxylate anion is not conjugated with the ring.

Hammett decided not to use the pK_as themselves for his correlation but defined a new parameter, which he called σ. This σ shows how electron-donating or -withdrawing a group is relative to H as a ratio of the logK_as or the difference of the pK_as between the substituent and benzoic acid itself. If the acid required to determine σ for a new substituent was not available, σ could be determined by correlation with other reactions. Here are the equations and the table of σ values for the most important substituents. A different value of σ for any given substituent was needed for the *meta* and the *para* positions and these are called σ_m and σ_p, respectively.

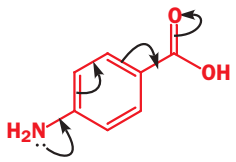
Substituent, X	pK_a of *p*-XC_6H_4COOH	pK_a of *m*-XC_6H_4COOH
NH_2	4.82	4.20
OCH_3	4.49	4.09
CH_3	4.37	4.26
H	4.20	4.20
F	4.15	3.86
I	3.97	3.85
Cl	3.98	3.83
Br	3.97	3.80
CO_2CH_3	3.75	3.87
$COCH_3$	3.71	3.83
CN	3.53	3.58
NO_2	3.43	3.47

$$\sigma_X = \log\left(\frac{K_a(X\text{–}C_6H_4COOH)}{K_a(C_6H_5COOH)}\right) = pK_a(C_6H_5COOH) - pK_a(X\text{–}C_6H_4COOH)$$

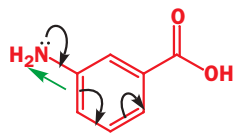
You need a general idea as to what a σ value means. If σ = 0 the substituent has no effect: it is electronically the same as H. If σ is positive, the substituent is electron-withdrawing. This is unfortunate perhaps, but just remember that the comparison is with acid strength. Positive σ means a stronger acid so the substituent is electron-withdrawing. The more positive the charge induced on the ring by a substituent, the larger its σ value. Negative σ means weaker acid and electron donation. Inductive effects from polarization of σ bonds are greater for σ_m than for σ_p because the substituent is nearer.

Conjugation is generally more effective in the *para* position (see Chapter 22) so $\sigma_p > \sigma_m$ for conjugating substituents. Indeed, the NH_2 group has a large negative σ_p and a zero σ_m. The NH_2 group donates electrons strongly to the carbonyl group of benzoic acid from the *para* position but does not conjugate in the *meta* position where its donation happens just to balance the effect of electronegative nitrogen.

The OMe group has a negative σ_p but a positive σ_m because a weaker electron donation from the lone pairs is more important in the *para* position but the effect of very elec-



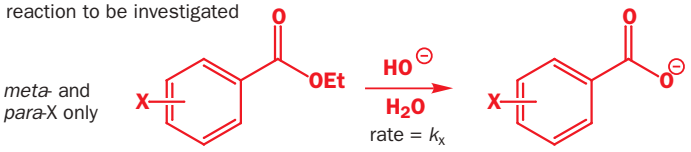
strong conjugation into carbonyl group: large negative σ_p



conjugation into ring not carbonyl group balances weak effect of electronegative N: zero negative σ_m

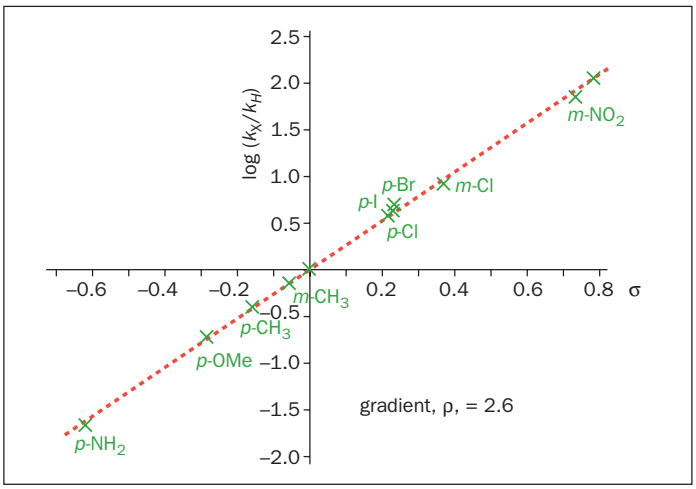
Substituent, X	σ_p	σ_m	Comments
NH_2	–0.62	0.00	groups that donate electrons have negative σ
OCH_3	–0.29	0.11	
CH_3	–0.17	–0.06	
H	0.00	0.00	there are no values for *ortho* substituents
F	0.05	0.34	
I	0.23	0.35	
Cl	0.22	0.37	$\sigma_p < \sigma_m$ for inductive withdrawal
Br	0.23	0.40	
CO_2CH_3	0.45	0.33	
$COCH_3$	0.49	0.37	$\sigma_p > \sigma_m$ for conjugating substituents
CN	0.67	0.62	
NO_2	0.77	0.73	groups that withdraw electrons have positive σ

tronegative oxygen on the σ framework of the ring in the *meta* position is more important than lone pair donation that doesn't reach the carbonyl group. You do not need to learn any σ values but you should be able to work out the sign of σ for well known substituents and estimate a rough value.



The Hammett reaction constant ρ

Now we can return to our reaction: the alkaline hydrolysis of various *meta*- and *para*-substituted ethyl benzoates. The rate constants for this second-order reaction have been measured and shown here is a graph of log (k_X/k_H) versus σ, where k_X is the rate constant for the reaction with the substituted benzoate and k_H is that for the unsubstituted reaction (X = H).

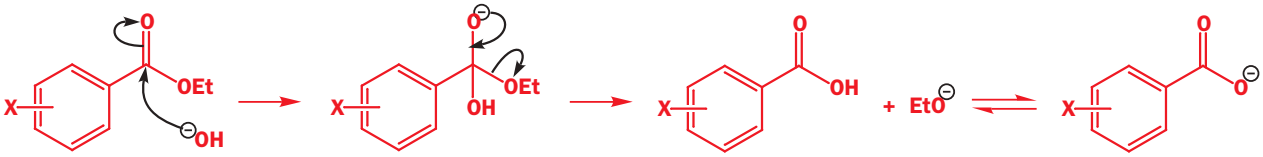


We can see straight away that there is a good correlation between how fast the reaction goes and the value of σ; in other words, the points lie more or less on a straight line. The gradient of this best fit line, given the symbol ρ (rho), tells us how sensitive the reaction is to substituent effects in comparison with the ionization of benzoic acids. The gradient is ρ = +2.6. This tells us that the reaction responds to substituent effects in the same way (because it is +) as the ionization of benzoic acids but by much more ($10^{1.6}$ times more) because it is 2.6 instead of 1.0. We already know what the mechanism of this reaction is.

▶ Getting to grips with logs

A difference between two values of *x* log units means the values actually differ by a factor of 10^x. From the graph for the hydrolysis of ethyl benzoates we can see that the *p*-NO_2 benzoate hydrolyses some 10^2 times faster than the unsubstituted benzoate, while the *p*-NH_2 benzoate hydrolyses some 10^2 times slower.

▶ Hammett chose σ (Greek s) for *substituent* and ρ (Greek r) for *reaction*.

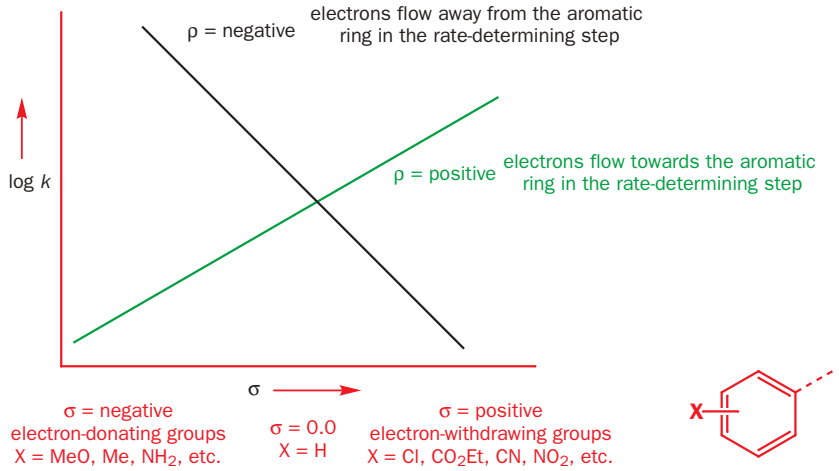


The first step is quite like the ionization of benzoic acid. A negative charge is appearing on the carbonyl oxygen atom and that negative charge will be stabilized by electron-withdrawing X groups. Provided that the first step is rate-determining, a positive ρ is fine. We cannot say much as yet about the value as we are comparing a reaction rate (for the hydrolysis) with an equilibrium position (for the ionization). It will help you a great deal if you think of *positive* ρ values as meaning an *increase* in electron density near to or on the benzene ring. They may mean the appearance of a negative charge but they may not. We need now to look at some other reactions to get a grasp of the meaning of the value of the Hammett ρ.

● The Hammett reaction constant ρ measures the *sensitivity* of the reaction to electronic effects.

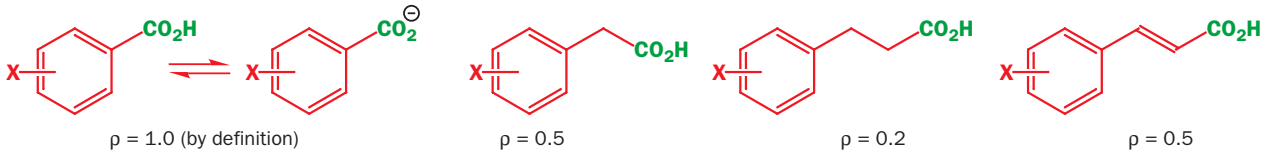
- A *positive* ρ value means *more* electrons in the transition state than in the starting material
- A *negative* ρ value means *fewer* electrons in the transition state than in the starting material

typical Hammett plots

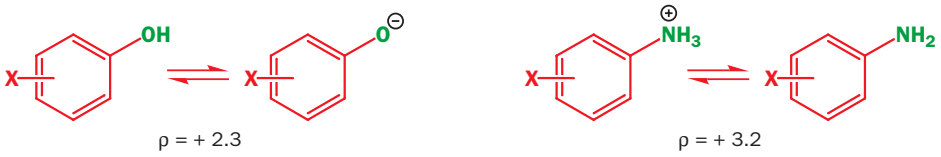


Equilibria with positive Hammett ρ values

We can compare these directly with the ionization of benzoic acids. If we simply move the carboxylic acid away from the ring, the ρ value for ionization gets less. This is just the effect of a more distant substituent. When there are two saturated carbons between the benzene ring and the carboxylic acid, there is almost no effect. When we are using the aromatic ring as a probe for a reaction mechanism, it must be placed not too far away from the reaction centre. However, if we restore electronic communications with a double bond, ρ goes back up again to a useful value.

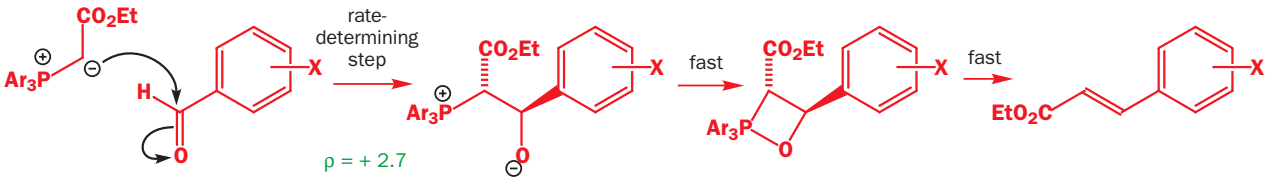


If the negative charge on the anion can actually be delocalized round the ring, as with substituted phenols, we should expect the size of ρ to increase. Both the phenol and the anion are delocalized but it is more important for the anion. The effect is larger for the ionization of anilinium salts as the acid ($ArNH_3^+$) does not have a delocalized lone pair but the conjugate base ($ArNH_2$) does.

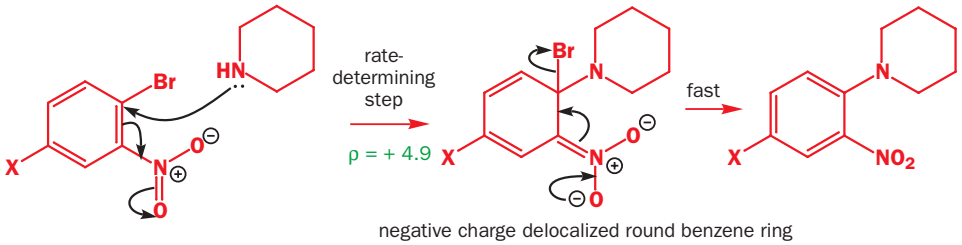


Reactions with positive Hammett ρ values

Any reaction that involves nucleophilic attack on a carbonyl group as the rate-determining step is going to have a ρ value of about 2–3, the same as for the hydrolysis of esters that we have already seen. Examples include the Wittig reaction of stabilized ylids (Chapters 14 and 31). Though there is some dispute over the exact mechanism of the Wittig reaction, the ρ value of 2.7 strongly suggests that nucleophilic attack on the aldehyde by the ylid is involved with stabilized ylids and aromatic aldehydes at least. In addition, there is a small variation of rate with the aryl group on phosphorus: if Ar = *p*-$MeOC_6H_4$ the reaction goes about six times faster than if Ar = *p*-ClC_6H_4. These groups are a long way from the reaction site but electron donation would be expected to accelerate the donation of electrons from the ylid.

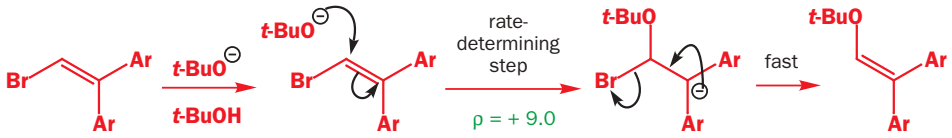


Large positive ρ values usually indicate extra electrons in the transition state delocalized into the ring itself. A classic example is nucleophilic aromatic substitution by the addition–elimination mechanism (Chapter 23). The ρ value is +4.9, but even this large value does not mean a complete anion on the benzene ring as the nitro group, present in all cases, takes most of the negative charge. The substituent X merely helps.



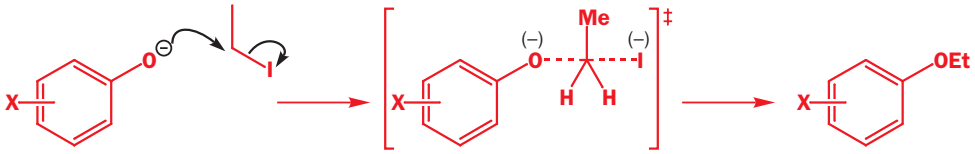
negative charge delocalized round benzene ring

We get the full value when there are no nitro groups to take the brunt of the negative charge. This vinylic substitution (an unusual reaction!) has a ρ value of +9.0. It cannot be an S_N2 reaction or it would have a small ρ value and it cannot be an S_N1 reaction or it would have a negative ρ value (fewer electrons in the transition state). It must be an addition–elimination mechanism through a benzylic anion delocalized round both benzene rings.



Reactions with negative Hammett ρ values

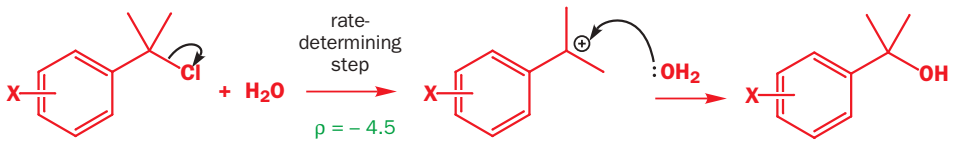
Negative ρ values mean electrons flowing away from the ring. A useful example is the S_N2 displacement of iodide from EtI by phenoxide anions. This has a ρ value of exactly –1.0. Though the transition state has a negative charge, that charge is decreasing on the aromatic ring as the starting material approaches the transition state.



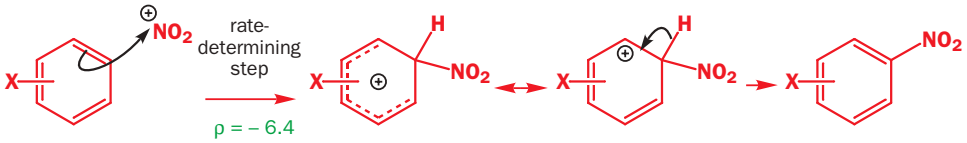
full negative charge delocalized round ring

partial negative charge delocalized round ring

An S_N1 reaction on the carbon atom next to the ring has a large negative ρ value. In this example, a tertiary benzylic cation is the intermediate and the rate-determining step is, of course, the formation of the cation. The cation is next to the ring but delocalized round it and the ρ value is –4.5, about the same value, though negative, as that for the nucleophilic substitution on nitrobenzenes by the addition–elimination mechanism that we saw in the last section.

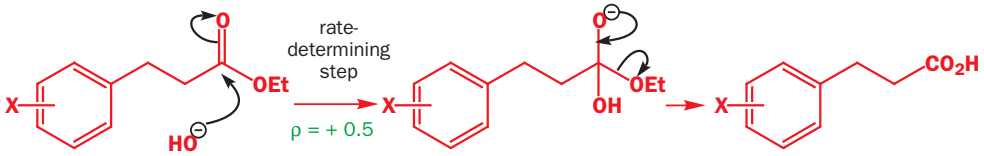


The largest negative ρ values come from electrophilic aromatic substitution (Chapter 22) where the electrons of the ring are used in the reaction leaving a positive charge on the ring itself in the intermediate. Some of this charge is already there in the transition state. Negative ρ values mean electrons flowing out of the ring. This simple nitration has ρ = – 6.4 and ρ values for electrophilic aromatic substitution are usually in the range –5 to –9.

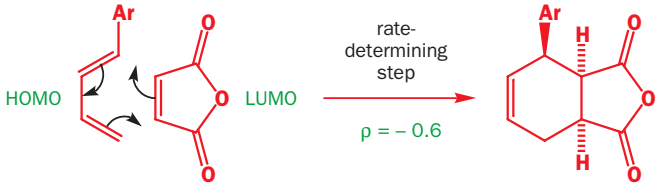


Reactions with small Hammett ρ values

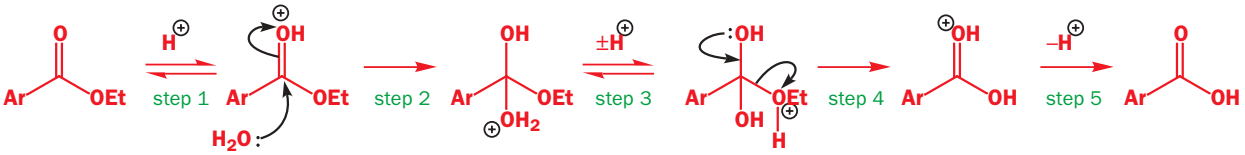
Small Hammett ρ values arise in three ways. The aromatic ring being used as a probe for the mechanism may simply be too far away for the result to be significant. This trivial case of the alkaline hydrolysis of the 3-aryl propionate ester has a ρ value of +0.5 and it is surprising that it is even that large.



The second case is the informative one where the reaction is not dependent on electrons flowing into or out of the ring. Pericyclic reactions are important examples and the Diels–Alder reaction of arylbutadienes with maleic anhydride shows a small negative ρ value of –0.6. The small value is consistent with a mechanism not involving charge accumulation or dispersal but the sign is interesting. We explained this type of Diels–Alder reaction in Chapter 35 by using the HOMO of the diene and the LUMO of the dienophile. The negative sign of ρ, small though it is, supports this view.



The third case is in many ways the most interesting. We have seen that the alkaline hydrolysis of ethyl esters of benzoic acids ($ArCO_2Et$) has a ρ value of +2.6 and that this is a reasonable value for a reaction involving nucleophilic attack on a carbonyl group conjugated with the aromatic ring. The hydrolysis of the same esters in acid solution, which also involves nucleophilic attack on the same carbonyl group, has a ρ value of +0.1. In other words, all these esters hydrolyse at the same rate in acid solution. Neither of the previous explanations will do. We need to see the full mechanism to explain this remarkable result.



Steps 1, 3, and 5 cannot be slow as they are just proton transfers between oxygen atoms (Chapter 13). That leaves only steps 2 and 4 as possible rate-determining steps. The bimolecular addition of the weak nucleophile water to the low concentration of protonated ester (step 2) is the most attractive candidate, as step 4—the unimolecular loss of ethanol and re-formation of the carbonyl group—should be fast. What ρ value would be expected for the reaction if step 2 were the rate-determining step? It would be made up of two parts. There would be an equilibrium ρ value for the protonation and a reaction ρ value for the addition of water. Step 1 involves electrons flowing out of the molecule and step 2 involves electrons flowing in so the ρ values for these two steps would have opposite charges. We know that the ρ value for step 2 would be about +2.5 and a value of about –2.5 for the equilibrium protonation is reasonable. This is indeed the explanation: step 2 is the rate-deter-

mining step and the ρ values for steps 1 and 2 almost cancel each other out. All steps before the rate-determining step are present in the rate equation and also affect the Hammett ρ value.

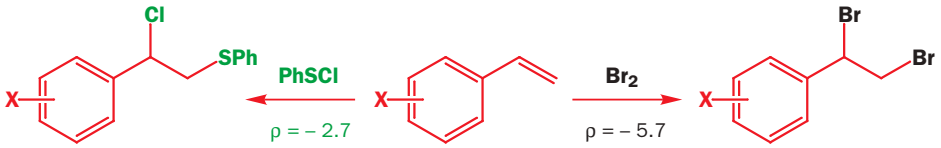
The meaning of Hammett ρ values

This then is the full picture. You should not, of course, learn these numbers but you need an idea of roughly what each group of values means. You should see now why it is unimportant whether the Hammett correlation gives a good straight line or not. We just want to know whether ρ is + or – and whether it is, say, 3 or 6. It is meaningless to debate the significance of a r value of 3.4 as distinct from one of 3.8.

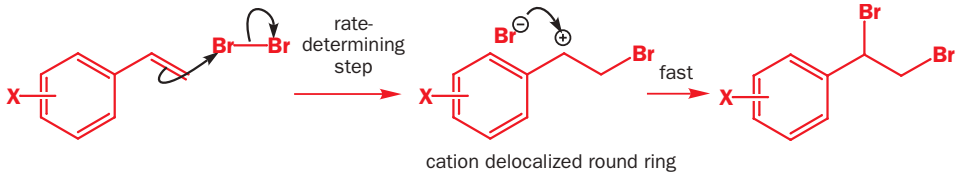
–6 –5	–4 –3 –2	–1 0 +1	+2 +3 +4	+5 +6
large negative ρ-values	moderate negative ρ-values	small ρ-values	moderate positive ρ-values	large positive ρ-values
positive charge on ring or delocalized round benzene ring	electrons flow out of TS positive charge near ring loss of conjugation	1. Ar too far away 2. No electron change 3. Two ρ-values cancel each other out	electrons flow into TS negative charge near ring loss of conjugation	negative charge on ring or delocalized round benzene ring

Using the Hammett ρ values to discover mechanisms

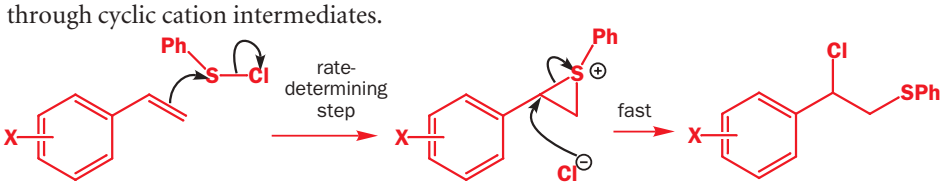
Electrophilic attack on alkenes by bromine often goes through three-membered ring cyclic bromonium ions and we can sometimes tell that this is so by studying the stereochemistry. Here are two reactions of styrenes that look very similar—a reaction with bromine and one with PhSCl. With no further information, we might be tempted to assume that they both go by the same mechanism. However, the Hammett ρ values for the two reactions are rather different.



The ρ value for bromination is definitely in the 'large' range and can only mean that a positive charge is formed that is delocalized round the benzene ring. Bromine evidently does not form a bromonium ion with these alkenes but prefers to form a secondary benzylic cation instead.



The sulfenylation, on the other hand, has a moderate negative ρ value. No cation is formed that is delocalized round the ring, but electrons flow out of the ring and we suspect some loss of conjugation. All this fits well with the formation of a three-membered ring intermediate. From experiments like this we learn that PhSCl is much more likely than bromine to react stereospecifically with alkenes through cyclic cation intermediates.

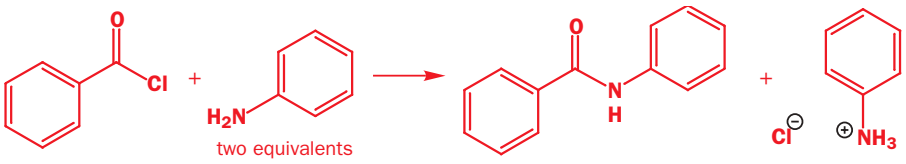


A complete picture of the transition state from Hammett plots

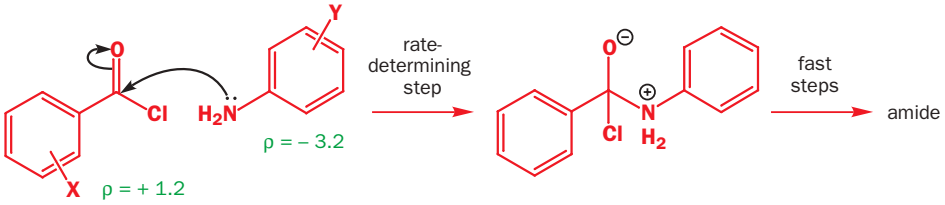
More information can be gained on the mechanism of the reaction if two separate experiments can be carried out with the mechanistic probe inserted at two different sites on the reagents. If we are studying a reaction between a nucleophile and an electrophile, it may be possible to make Hammett plots from the variation of substituents on both reagents. The acylation of amines with acid chlorides is an example.

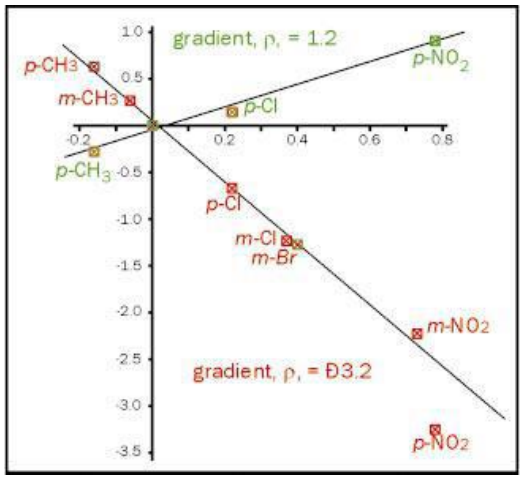
■ Chapter 20 gives a full description of these mechanisms.

■ There is more about these sulfenyl chlorides in Chapter 46.



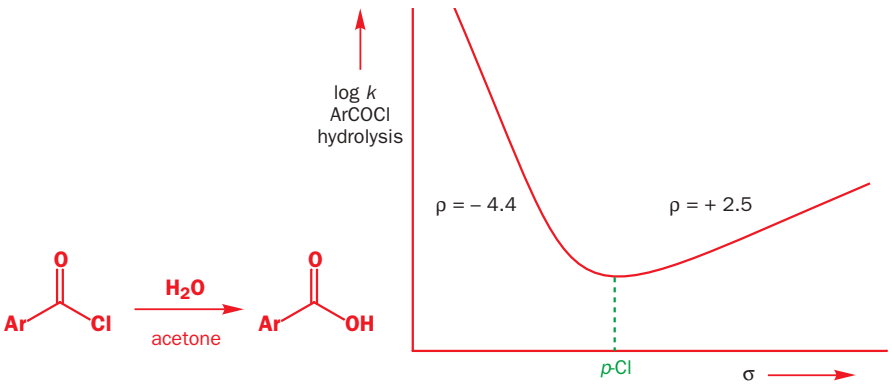
If we vary the structure of the acid chloride we get a ρ value of +1.2, suitable for nucleophilic attack on the carbonyl group. If we vary the amine we get a ρ value of –3.2, again suitable for electrons that were conjugated round the ring moving away to form a new bond. The simple answer is correct but the rate depends on the nucleophilicity of the amine 100 times more than on the electrophilicity of the acid chloride.



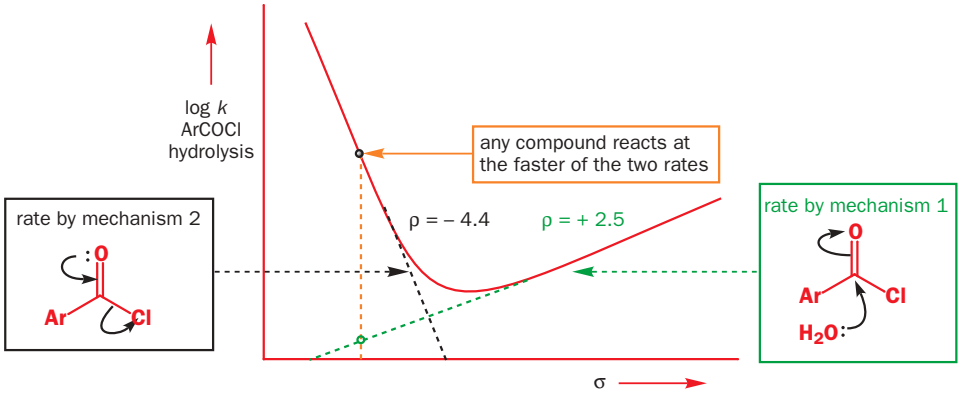


Nonlinear Hammett plots

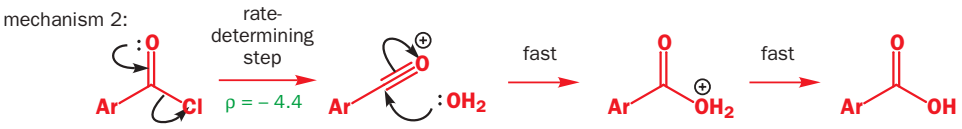
If we look at the hydrolysis of the acid chlorides of benzoic acids in aqueous acetone, we see a very odd Hammett plot indeed. You know that Hammett plots need not be perfectly linear but this one is clearly made up of two intersecting straight lines. This might look like disaster at first but, in fact, it gives us extra information. The right-hand part of the curve, for the more electron-withdrawing substituents, has a slope of +2.5: just what we should expect for rate-determining attack of water on the carbonyl group. As we go to less electron-withdrawing substituents, the rate of the reaction suddenly starts to increase as we pass the *para*-chloro compound and the left-hand part of the curve has a slope of –4.4.



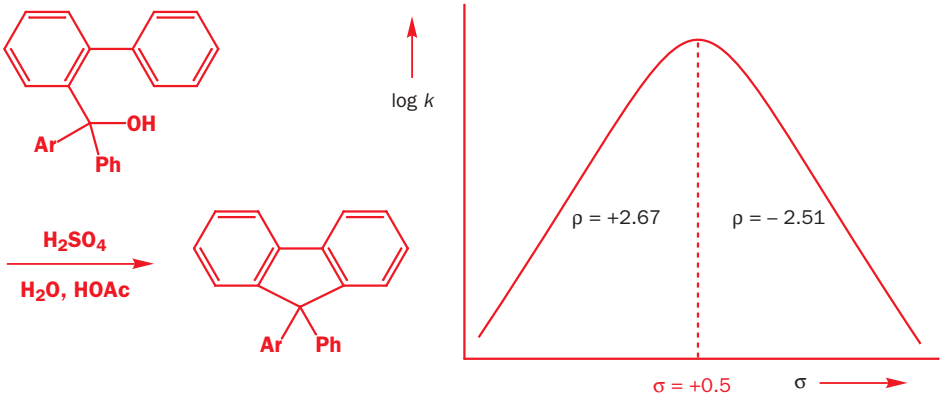
What can this mean? If the reaction becomes faster as we pass the discontinuity in the curve—and it gets faster whether we go from right to left or left to right—there must be a change in mechanism. If there is a choice between two mechanisms, the faster of the two will operate. Mechanism 1 is the rate-determining nucleophilic attack by water on the carbonyl group.



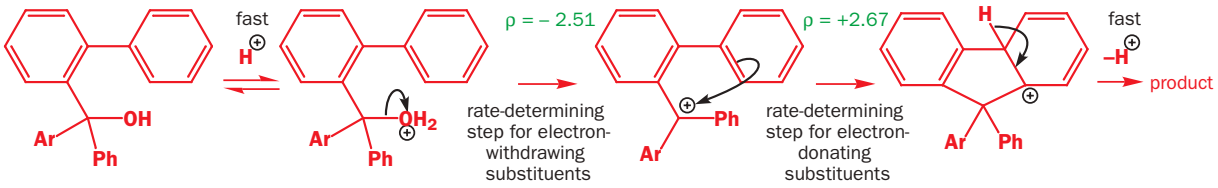
The new mechanism goes faster for more electron-donating substituents and has quite a large negative ρ value suggesting the formation of a cation in the rate-determining step. This mechanism (mechanism 2) must surely be the S_N1-like process of preliminary formation of an acylium ion by loss of chloride ion.



When the Hammett plot bends the other way, so that the rate of the reaction decreases as it passes the discontinuity, we have a single mechanism with a change in rate-determining step. A reaction goes by the fastest possible mechanism but its rate is limited by the slowest of the steps in that mechanism. An example is the intramolecular Friedel–Crafts alkylation of a diphenyl derivative where the alkylating agent is a diarylmethanol attached to one of the benzene rings in the *ortho* position.



The carbocation intermediate in the Friedel–Crafts reaction (Chapter 22) is rather stable, being tertiary and benzylic, and the formation of the cation, normally the rate-determining step, with inevitably a negative ρ value, goes faster and faster as the electron-donating power of the substituents increases until it is faster than the cyclization which becomes the rate-determining step. The cyclization puts electrons back into the carbocation and has a positive ρ value. As the two steps have more or less the reverse electron flow to and from the same carbon atom, it is reasonable for the size of ρ to be about the same but of opposite sign.



A reaction occurs by the faster of two possible mechanisms but by the slower of two possible rate-determining steps.

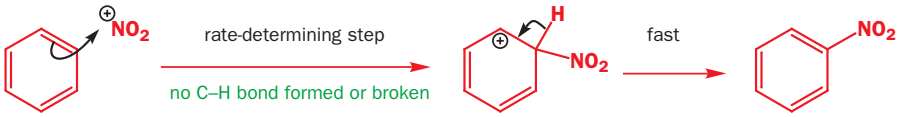
We shall see more examples of Hammett ρ values used in conjunction with other evidence as the chapter develops but now it is time to look at what other evidence is available.

Other kinetic evidence

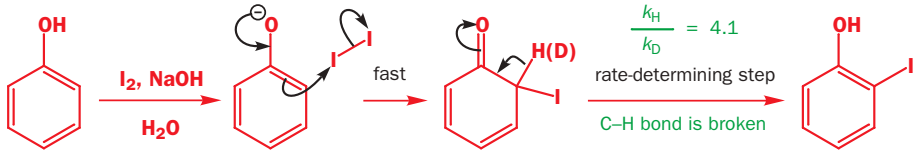
The kinetic deuterium isotope effect

Other kinetic isotope effects are known but they are very small: D is twice as heavy as H but ^{13}C only slightly heavier than ^{12}C.

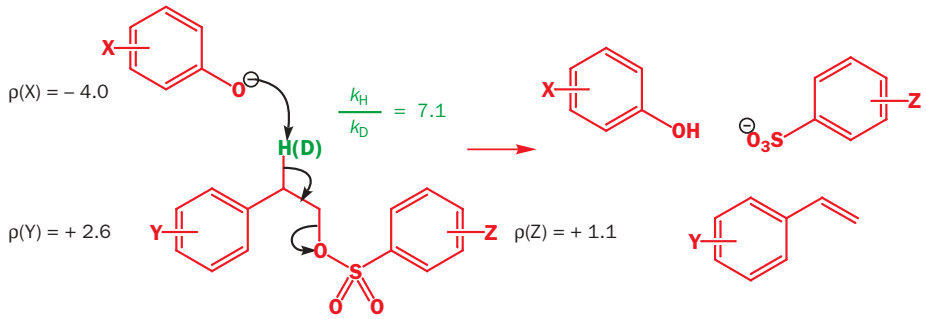
The kinetic isotope effect was introduced in Chapter 19. If a bond to deuterium is formed or broken in the rate-determining step of a reaction, the deuterated compound will react more slowly, usually by a factor of about 2–7. This effect is particularly valuable when C–H bonds are being formed or broken. In Chapter 22 we told you that the rate-determining step in the nitration of benzene was the attack of the electrophile on the benzene ring. This is easily verified by replacing the hydrogen atoms round the benzene ring with deuteriums. The rate of the reaction stays the same.



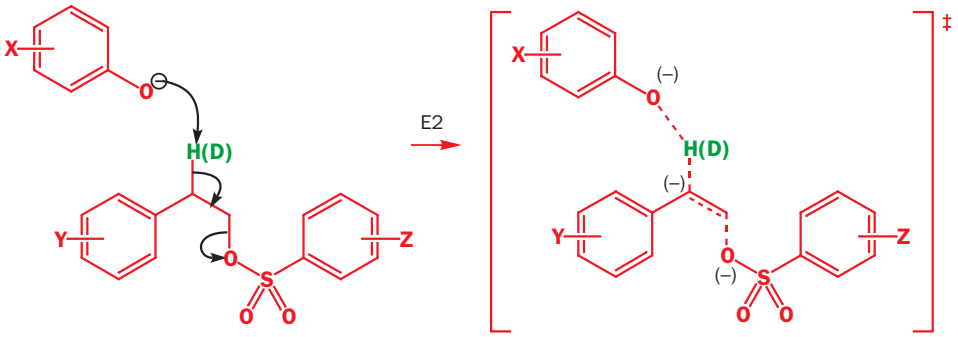
If the second step, which does involve the breaking of a C–H bond, were the rate-determining step it would go more slowly if the H were replaced by D. In this case the deuterium isotope effect is $k_H/k_D = 1.0$. If the reaction is the iodination of phenol in basic solution, there is a deuterium isotope effect of $k_H/k_D = 4.1$. Clearly, the other step must now be the rate-determining step—the phenolate ion reacts so rapidly that the first step is faster than the second.



The deuterium isotope effect can add to the information from Hammett plots in building up a picture of a transition state. Three separate Hammett ρ values can be measured for this elimination reaction and this information is very valuable. But it would be sadly incomplete without the information that a large deuterium isotope effect $k_H/k_D = 7.1$ is observed for the hydrogen atom under attack.

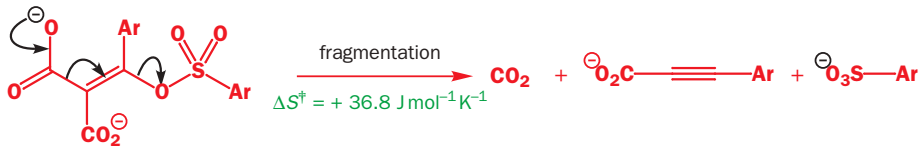


In this E2 reaction, it is no surprise that the base (ArO^-) donates electrons and the leaving group (ArO_3^-) accepts them. But the large deuterium isotope effect and moderate positive ρ(Y) value for an aromatic ring that might have done nothing suggest some build-up of negative charge in the transition state on that carbon atom as well as on the two oxygen atoms.

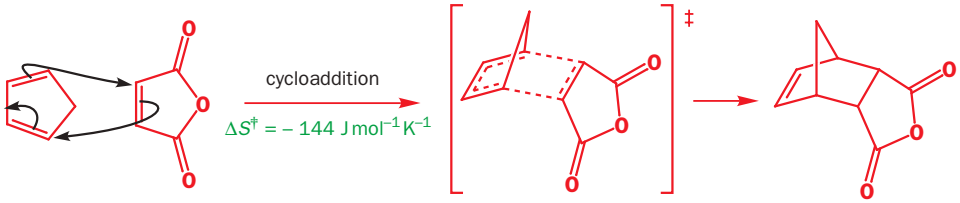


Entropy of activation

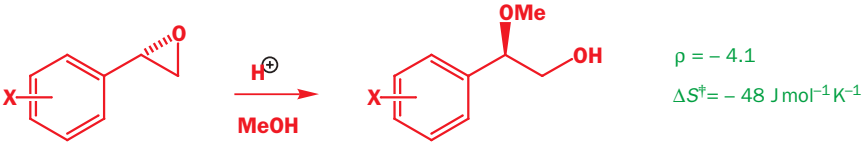
Of all the enthalpies and entropies that we introduced in Chapter 13, the entropy of activation, $\Delta S^{\ddagger}$, is by far the most useful. It tells us about the increase or decrease in order in a reaction as the starting material goes to the transition state. A positive $\Delta S^{\ddagger}$ means an increase in entropy or a decrease in order and a negative $\Delta S^{\ddagger}$ means an increase in order. Normally, unimolecular reactions in which one molecule gives two products have a positive $\Delta S^{\ddagger}$ and bimolecular reactions have a negative $\Delta S^{\ddagger}$. Fragmentations (Chapter 38) such as this decarboxylation in which one molecule fragments to three have positive $\Delta S^{\ddagger}$s. It has $\Delta S^{\ddagger} = +36.8\ J\ mol^{-1}\ K^{-1}$.



At the other extreme are cycloadditions (Chapter 35) such as the Diels–Alder reaction we examined a few pages back. Not only do two reagents become one product but a very precise orientation is required in the transition state usually meaning a large negative $\Delta S^{\ddagger}$. Diels–Alder reactions usually have $\Delta S^{\ddagger}$ of about –120 to –160 $J\ mol^{-1}\ K^{-1}$. The classic cyclopentadiene addition to maleic anhydride has $\Delta S^{\ddagger} = -144\ J\ mol^{-1}\ K^{-1}$.

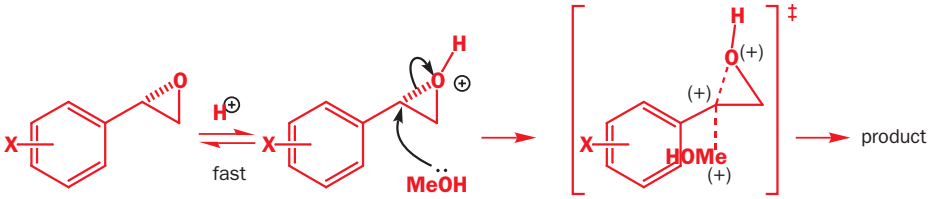


These numbers give you the range of entropies of activation you may expect to find. Large negative numbers are common but only small positive numbers are found. The largest negative numbers apply to bimolecular reactions where neither reagent is in great excess. Smaller negative numbers may mean a bimolecular reaction with solvent or some other reagent in large excess. The acid-catalysed opening of styrene oxides in methanol is a good example.



▶ Entropies of activation are measured in units of $J\ mol^{-1}\ K^{-1}$. All the values in this book are in $J\ mol^{-1}\ K^{-1}$ but in older books you will see 'entropy units' (e.u.), which are $cal\ mol^{-1}\ K^{-1}$. Values in e.u. should be multiplied by about

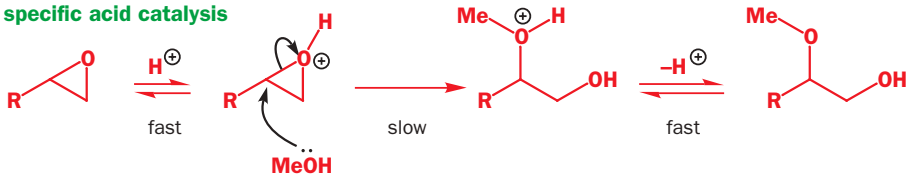
The Hammett ρ value of –4.1 suggests a carbocation intermediate as does the regioselectivity of the reaction (MeOH attacks the benzylic position) but the stereochemistry (the reaction occurs with inversion) and a modest negative entropy of activation ($\Delta S^{\ddagger} = -48\ \mathrm{J\,mol^{-1}\,K^{-1}}$) suggest rather an S_N2 reaction with a loose transition state having substantial positive charge at the benzylic carbon. Neither piece of evidence alone would be enough to define the mechanism.



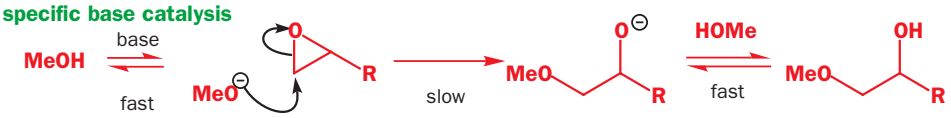
This example with its acid catalyst brings us to the subject of catalysis. We must now analyse the different sorts of acid and base catalysis and see how the mechanisms can be distinguished using the methods we have discussed.

Acid and base catalysis

Acids and bases provide the best known ways of speeding up reactions. If you want to make an ester—add some acid. If you want to hydrolyse an ester—add some base. It may all seem rather simple. However, there are actually two kinds of acid catalysis and two kinds of base catalysis and this section is intended to explain the difference in concept and how to discover which operates. When we talk about acid catalysis we normally mean **specific acid catalysis**. This is the kind we have just seen—epoxides don't react with methanol but, if we protonate the epoxide first, then it reacts. Specific acid catalysis protonates electrophiles and makes them more electrophilic.



We could, on the other hand, have argued that methanol is not a good enough nucleophile but if deprotonated with a base it becomes the much more nucleophilic methoxide. This is **specific base catalysis**.

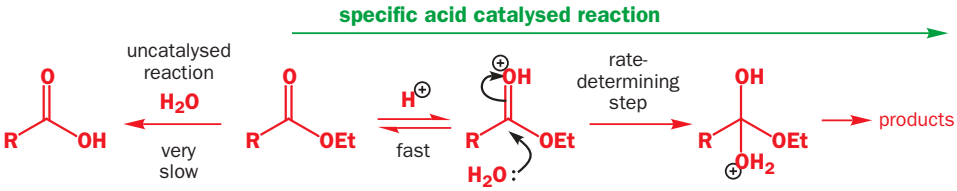


We shall discuss these two types first because they are straightforward. You need to recognize their characteristics, their strengths, and their weaknesses. We hope you will get into the habit of recognizing these types of catalysis so that you hardly have to think about it—it should become second nature.

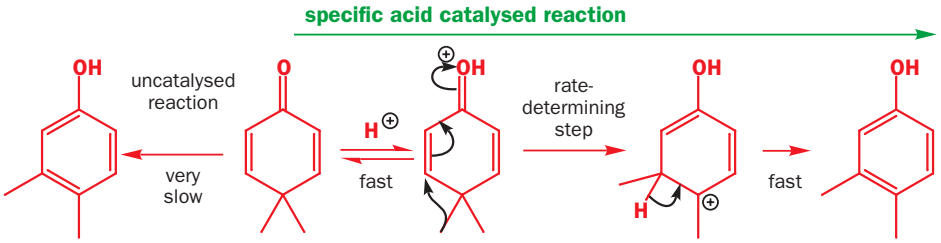
Specific acid catalysis

► SAC is the usual method by which acids make reactions go faster and, if you think about the acid-catalysed reactions you already know, you will see that you have been using it all along without realizing it.

Specific acid catalysis (SAC) involves a rapid protonation of the compound followed by the slow step, which is accelerated in comparison with the uncatalysed reaction because of the greater reactivity of the protonated compound. You have just seen an example with an epoxide. Ester hydrolysis (or formation) is another. Water attacks esters very slowly: it attacks protonated esters much more quickly. This is just the ordinary mechanism for acid-catalysed ester hydrolysis (or formation) given in Chapter 12.



A more interesting reaction is the dienone–phenol rearrangement (Chapter 37). Rearrangement in the absence of acid is very slow but, once the ketone oxygen is protonated, it occurs very rapidly. Again we have fast equilibrium protonation followed by a rate-determining step involving a reaction of the protonated species and again this is the ordinary mechanism that you now know to call SAC.



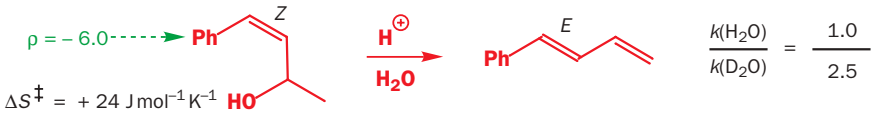
This catalysis depends only on the protonating power of the solution. The compound must be protonated to react so the catalyst must be a strong enough acid to do the job. It is not necessary that every molecule is protonated, just enough to set the reaction going as the acid is regenerated at the end. So the (log of the) rate of the reaction is inversely proportional to the pH of the solution and significant only in the region of, and of course below, the pK_{aH} of the substrate.

There is one special experimental indication of this mechanism. If the reaction is carried out in a deuterated solvent (D_2O instead of H_2O) the rate of the reaction increases. This is a solvent isotope effect rather than a kinetic isotope effect and needs some explanation. If you examine the three examples of SAC in the previous pages you will see that they share these characteristics: a fast proton exchange is followed by a rate-determining step that does *not* involve the making or breaking of any bonds to hydrogen. In general terms:

The rate of the reaction is the rate of the rate-determining step: rate = $k[XH^+]$. The concentration of the intermediate $[XH^+]$ is related to the pH and to the concentration of the substrate by the equilibrium constant, K, of the protonation. So we have: rate = $kK[H^+][X]$. We know that k does not change when hydrogen is replaced by deuterium so K must increase in D_2O.

You will sometimes see in books the statement that D_3O^+ is a stronger acid than H_3O^+. This is partly true. The full truth is that D_3O^+ *in* D_2O is a stronger acid than H_3O^+ *in* H_2O. Water (H_2O) is a better solvating agent for H_3O^+ than D_2O is for D_3O^+, simply because it forms stronger hydrogen bonds due to the greater O–H vibration frequency. So D_3O^+ in D_2O is less well solvated than H_3O^+ in H_2O and is a stronger acid. You need an example.

The *Z*-allylic alcohol below dehydrates in acid solution to the *E*-diene. We have lots of data on this mechanism, all summarized in the diagrams. You may like to note as well that the product contains no deuterium after dehydration in D_2O.

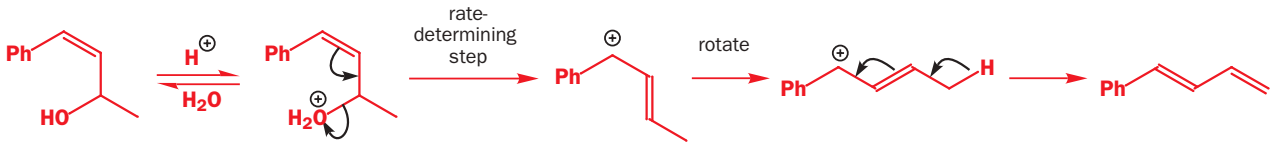


The Hammett ρ value of –6.0 suggests a carbocation intermediate and the positive entropy of activation suggests a rate-determining step in which disorder increases, perhaps one molecule breaking into two. The inverse solvent deuterium isotope effect (faster reaction in D_2O than in H_2O) strongly suggests SAC. Putting all this together we have a mechanism—a simple example of SAC with no protonation at carbon.

▶ A normal kinetic isotope effect has $k_H/k_D > 1$. Deuterium is often put into compounds by exchange with the cheapest source, D_2O, so reactions in D_2O often go slower than reactions in H_2O. Reactions with $k_H/k_D < 1$ have inverse deuterium isotope effects so a reaction that goes faster in D_2O than in H_2O (even when that is the expected pattern) has an *inverse* solvent deuterium isotope effect.

▶ It is not, of course, possible to use D_3O^+ in H_2O as H and D exchange very quickly. The solvent determines which acid is present.

■ You might like to compare this mechanism with the isomerization of the same diene described earlier in this chapter.



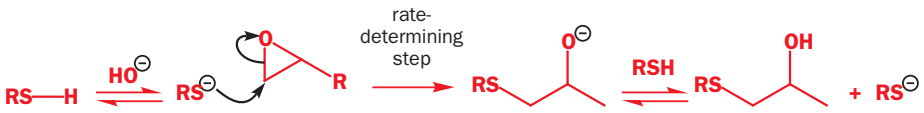
One more thing about this example. The rate-determining step is the second step so the other data, the Hammett ρ value and the entropy of activation, also refer to the combination of K and k. The equilibrium ρ value for the protonation will be fairly small and negative as a positive charge is being created some way from the benzene ring. The kinetic ρ value for the loss of water will be large and negative because a positive charge is being created that is delocalized into the ring. A combined value of –6 looks fine. The equilibrium entropy ΔS^o for the protonation will probably be small and negative as $ROH + H_3O^+ \rightleftharpoons ROH_2^+ + H_2O$ represents little change in order (two molecules going to two) and the $\Delta S^{\ddagger}$ for the loss of water will be large and positive (one molecule going to two) so a small positive value is about right. It doesn't do to interpret these numbers too closely.

Summary of features of specific acid catalysis

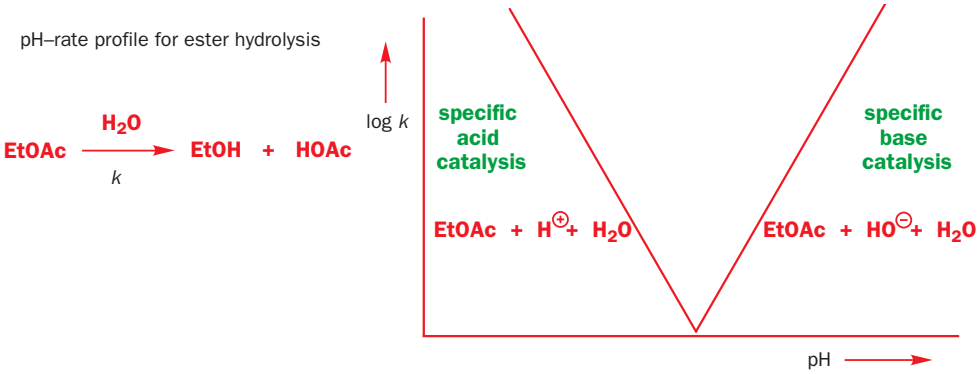
1. Only H_3O^+ is an effective catalyst; pH alone matters
2. Usually means rate-determining reaction of protonated species
3. Effective only at pHs near or below the pK_{aH} of the substrate
4. Proton transfer is not involved in the rate-determining step
5. Only simple unimolecular and bimolecular steps—moderate + or $-\Delta S^{\ddagger}$
6. Inverse solvent isotope effect $k(H_2O) < k(D_2O)$

Specific base catalysis

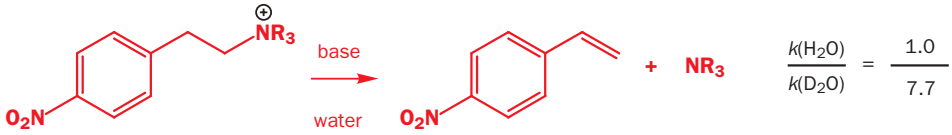
The other side of the coin is specific base catalysis (SBC) which usually involves the removal of a proton from the substrate in a fast pre-equilibrium step followed by a rate-determining reaction of the anion. Most of the base-catalysed reactions you are familiar with work by SBC. Examples include opening of epoxides with thiols.



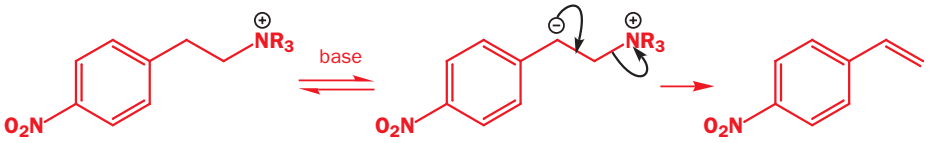
The rate of the reaction depends on the pH of the solution. If it is around or higher than the pK_a of the thiol, thiolate anion will be formed and this opens the epoxide much faster than does the unionized thiol. The nucleophile is regenerated by the oxyanion produced in the rate-determining step. A more familiar example is the base-catalysed hydrolysis of esters we have mentioned several times in this chapter. The full pH–rate profile (Chapter 13) for the hydrolysis of a simple ester such as ethyl acetate shows just two straight lines meeting each other (and zero rate) at about neutrality. Ethyl acetate hydrolysis occurs by SAC or SBC only.



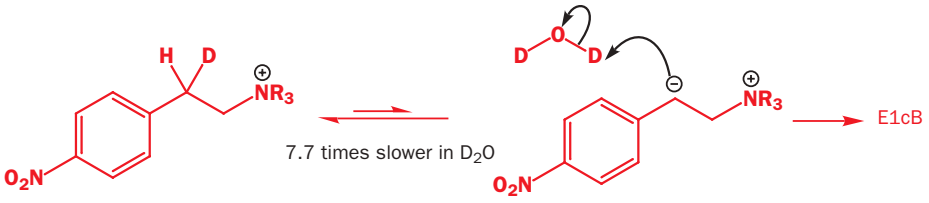
Removal of a proton from heteroatoms by heteroatom bases is always a fast step but removal of a proton from carbon can be the rate-determining step. A remarkably large inverse solvent deuterium isotope effect was found with this elimination of a tertiary amine in basic solution.



The detailed mechanism cannot, of course, be E2 or the isotope effect, if any, would be the other way round. If it is SBC, the mechanism then becomes the well-known E1cB (Chapter 19) having a carbanion as intermediate.



But 1/7.7 is too large to be a solvent isotope effect and looks much more like a normal kinetic isotope effect. And so it is. The tertiary amine is not a very good leaving group in spite of its positive charge (pK_{aH} about 10) so the carbanion mostly reverts to starting materials. The isotope effect is a kinetic isotope effect on this reverse step—the protonation of the carbanion. This reaction involves a proton transfer from H_2O or D_2O and will be much faster (could be 7.7 times) in H_2O by the ordinary kinetic isotope effect. The *elimination* reaction goes faster in D_2O because the back reaction goes more slowly and more of the carbanion goes on to product.



▶Microscopic reversibility

There is only one least-energy pathway between two interconverting compounds such as the starting material and the intermediate here. Every microscopic detail of the back reaction is exactly the same as that for the forward reaction. This is the principle of microscopic reversibility. Here we use evidence from the back reaction (slow proton transfer from water to the carbanion) to tell us about the forward reaction. This principle will be useful in Chapter 42.

● Summary of features of specific base catalysis

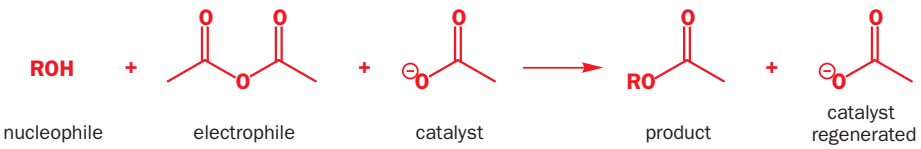
1. Only HO^- is an effective catalyst; pH alone matters
2. Usually means rate-determining reaction of deprotonated species
3. Effective only at pHs near or above the pK_a of the substrate
4. Proton transfer is not involved in the rate-determining step, unless C–H bonds are involved
5. Only simple unimolecular and bimolecular steps—moderate + or $-\Delta S^{\ddagger}$
6. Inverse solvent isotope effect $k(H_2O) < k(D_2O)$

General acid/base catalysis

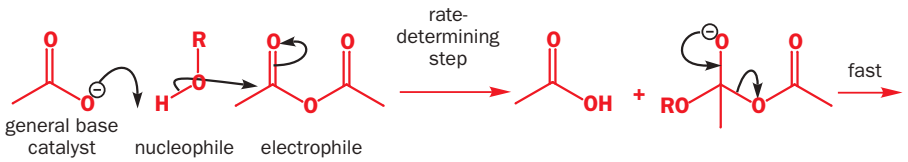
The other kind of acid/base catalysis is called 'general' rather than 'specific' and abbreviated GAC or GBC. As the name implies this kind of catalysis depends not only on pH but also on the concentration of undissociated acids and bases other than hydroxide ion. It is a milder kind of catalysis and is used in living things. The proton transfer is not complete before the rate-determining step but occurs during it. A simple example is the catalysis by acetate ion of the formation of esters from alcohols and acetic anhydride.

■

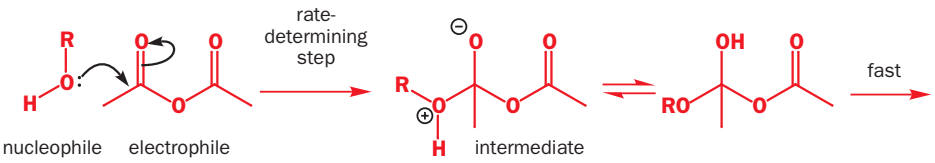
There was some discussion of this reaction in Chapter 13. Chapter 12 refers to the difficulty of pinpointing proton transfers in mechanisms involving the carbonyl group.



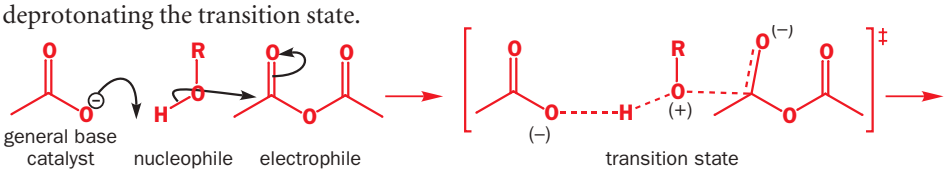
How can this catalysis work? At first sight there seems to be no mechanism available. Acetate cannot act as a specific base—it is far too weak (pK_{aH} 4.7) to remove a proton from an alcohol (pK_a about 15). If it acted as a nucleophile (Chapters 12 and 13) there would be no catalysis as nucleophilic attack on acetic anhydride would be a nonreaction simply regenerating starting materials. The only thing it can do is to remove the proton from the alcohol *as the reaction occurs.*



You will see at once that there is a great disadvantage in this mechanism: the rate-determining step is termolecular and this is really termolecular—three molecules colliding—and not just some mathematical kinetic trick. This comes out most clearly in the entropy of activation which is an enormous negative value, around $\Delta S^{\ddagger} = -168\ \mathrm{J\,mol^{-1}\,K^{-1}}$ for this reaction. There will also be a normal kinetic isotope effect for ROD against ROH as a bond to hydrogen is being formed and broken in the rate-determining step: it is $k_H/k_D = 2.4$ here. These GBC or GAC reactions are normally effective only if one of the three molecules is present in large excess—this reaction might be done in ROH as a solvent, for example, so that ROH is always present. In understanding how this GBC works it is helpful to look at the mechanism without catalysis.



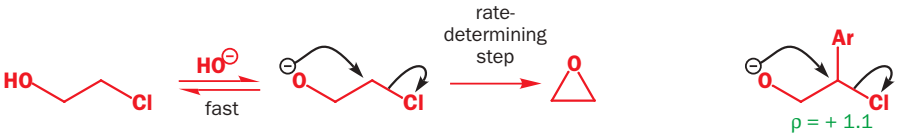
The acetate catalyst cannot remove a proton from the starting material but it can easily remove a proton from the intermediate, which has a complete positive charge on the alcohol oxygen atom. The starting material has a pK_a above the pK_{aH} of acetate but the product has a pK_a well below it. Somewhere in the middle of the rate-determining step, the pK_a of the ROH proton passes through the pK_{aH} of acetate and then acetate is a strong enough base to remove it. The GBC is effectively deprotonating the transition state.



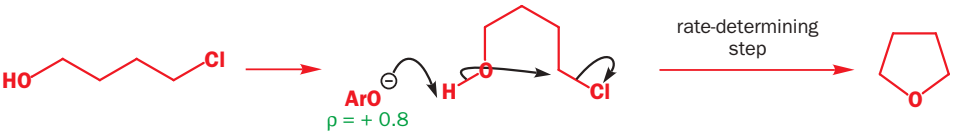
So how do we find GAC or GBC? Normally, general species catalysis is a weak addition to specific catalysis. We must remove that more powerful style of catalysis by working at a specific pH because SAC or SBC depends on pH alone. If we find that the rate of the reaction changes with the concentration of a weak base at constant pH, we have GBC. Note that, if the proton transfer is between heteroatoms, as in this example, some other bond-making or bond-breaking steps must be happening too as proton transfer between heteroatoms is always a fast process. Proton transfer to or from carbon can be slow.

The formation of three- and five-membered cyclic ethers shows the contrast between GBC and SBC. The formation of epoxides is straightforward SBC with a simple linear dependence on pH between pH 8 and 12 and no acceleration at constant pH by carbonate (CO_3^{2-}) ions. There is an

inverse solvent isotope effect and an aryl substituent at the electrophilic carbon atom gives the small positive ρ value expected for S_N2 with an anion.



Formation of tetrahydrofuran (THF) is also faster at higher pH but, by contrast, is also accelerated by various bases at constant pH. If anions of phenols (ArO^-) are used as catalysts, a Hammett ρ value of +0.8 shows that electrons are flowing away from the aromatic ring. There is a small normal kinetic isotope effect k_H/k_D = 1.4. There is SBC and GBC in this reaction. Here is the mechanism with ArO^- as GBC.



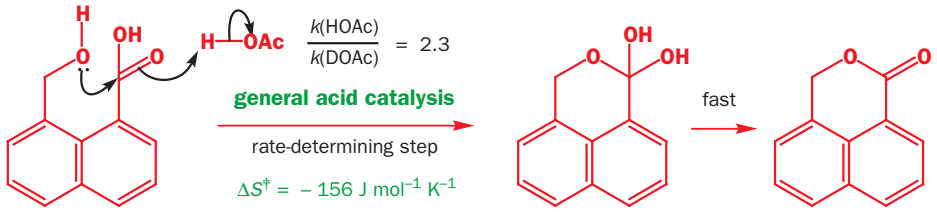
Why are the two different? The THF is easy to form, the transition state is unstrained, and only a little help is needed to make the reaction go. The epoxide is very strained indeed and the starting material needs to be raised in energy before cyclization will occur. Only the most powerful catalysis is good enough.

Summary of features of general base catalysis

1. Any base is an effective catalyst; pH also matters
2. Proton transfer is involved in the rate-determining step
3. Effective at neutral pHs even if below the pK_a of the substrate
4. Catalyst often much too weak a base to deprotonate reagent
5. Catalyst removes proton, which is becoming more acidic in the rate-determining step
6. Some other bond-making or bond-breaking also involved unless proton is on carbon
7. Often termolecular rate-determining step: large $-\Delta S^{\ddagger}$
8. Normal kinetic isotope effect k(H) > k(D)

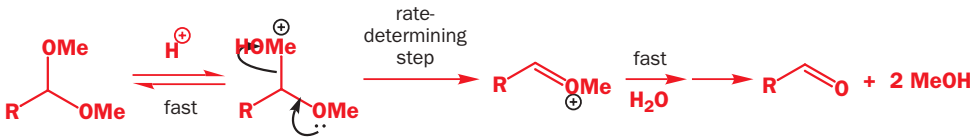
General acid catalysis

We have already discussed this in general terms so a couple of examples will be enough. First, the termolecular problem can be avoided if the reaction is intramolecular. The catalysis is then bimolecular as in the cyclization of this hydroxy-acid. Normally, ester formation and hydrolysis are specific-acid-catalysed only but here there is catalysis by acetic acid; k(HOAc)/k(DOAc) is 2.3 showing that proton transfer occurs in the rate-determining step and there is a large negative $\Delta S^{\ddagger}$ = –156 J mol^{-1} K^{-1}. This is general acid catalysis of nucleophilic attack on a carbonyl group, admittedly in a special molecule.



Earlier in the book (Chapter 14) we emphasized the importance of the mechanism for the formation and hydrolysis of acetals. These are SAC reactions: alcohols are bad leaving groups and usually need to be fully protonated by strong acids before they will go, even with the help of a lone pair on another oxygen atom.

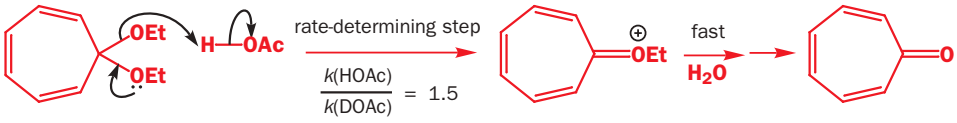
specific acid-catalysed acetal hydrolysis



■ In both these examples the steps after the rate-determining step are omitted and you should look at Chapter 14 for the full details.

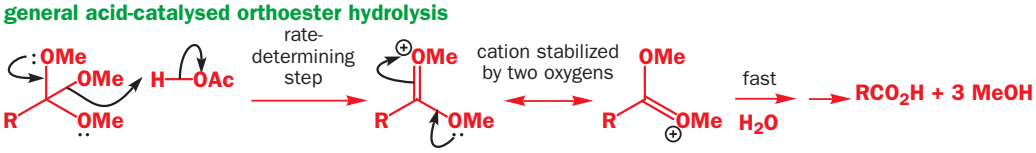
If we speed up the slow step by adding to the molecule some feature that stabilizes the cation intermediate, general acid catalysis may be found. One example is the aromatic cation formed in the hydrolysis of cycloheptatrienone acetals. The normal kinetic isotope effect proclaims GAC.

general acid-catalysed acetal hydrolysis



Even adding one extra alkoxy group so that we have an orthoester instead of an acetal is enough. These compounds show catalysis with a variety of weak acids at not very acidic pHs (5–6). As one OMe group is protonated, two others are pushing it out and they both help to stabilize the intermediate cation. Nature prefers these milder methods of catalysis as we will see in Chapter 50.

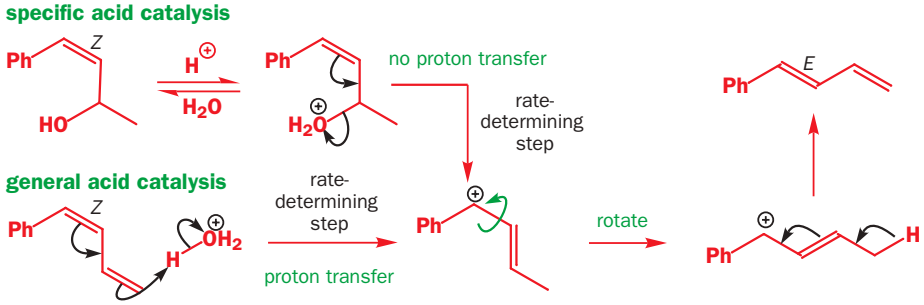
general acid-catalysed orthoester hydrolysis



For another contrast between SAC and GAC we need only refer you back to the two *Z*/*E* isomerizations earlier in the chapter. Isomerization of the diene is GAC—protonation at carbon is the slow step—and isomerization of the allylic alcohol is SAC. What we didn't tell you earlier was that the GAC reaction has a normal kinetic isotope effect of $k(\mathrm{H})/k(\mathrm{D}) = 2.5$ and a negative entropy of activation $\Delta S^{\ddagger} = -36\ \mathrm{J\,mol^{-1}\,K^{-1}}$—just what we should expect for a bimolecular reaction involving rate-determining proton transfer from oxygen to carbon. Notice that the intermediate cation is the same whichever the route; only the ways of getting there, including the rate-determining steps, are different.

specific acid catalysis

general acid catalysis



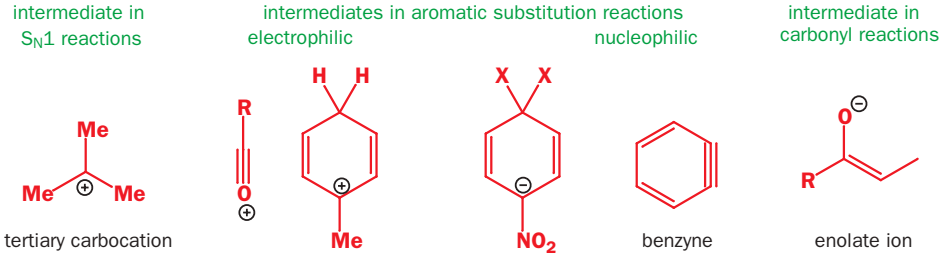
These examples show you that general acid catalysis is possible with strong acids, especially when protonation is at carbon and that, when protonation is at carbon, no other bond-making or -breaking steps need be involved.

Summary of features of general acid catalysis

1. Any acid is an effective catalyst; pH also matters
2. Proton transfer is involved in the rate-determining step
3. Effective at neutral pHs even if above the pK_{aH} of the substrate
4. Catalyst often much too weak an acid to protonate reagent
5. Catalyst adds proton to a site that is becoming more basic in the rate-determining step
6. Some other bond-making or bond-breaking also involved unless proton is on carbon
7. Often termolecular rate-determining step: large $-\Delta S^{\ddagger}$
8. Normal kinetic isotope effect $k(\mathrm{H}) > k(\mathrm{D})$

The detection of intermediates

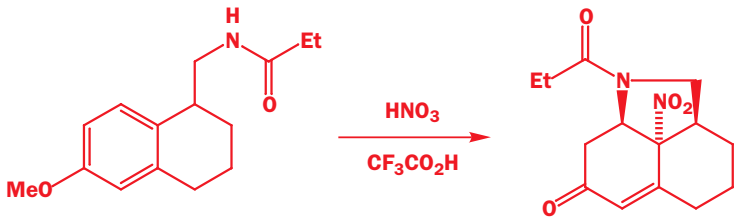
In earlier chapters we revealed how some reactive intermediates can be prepared, usually under special conditions rather different from those of the reaction under study, as a reassurance that some of these unlikely looking species can have real existence. Intermediates of this kind include the carbocation in the S_N1 reaction (Chapter 17), the cations and anions in electrophilic (Chapter 22) and nucleophilic (Chapter 23) aromatic substitutions, and the enols and enolates in various reactions of carbonyl compounds (Chapters 21 and 26–29). We have also used labelling in this chapter to show that symmetrical intermediates are probably involved in, for example, nucleophilic aromatic substitution with a benzyne intermediate (Chapter 23).



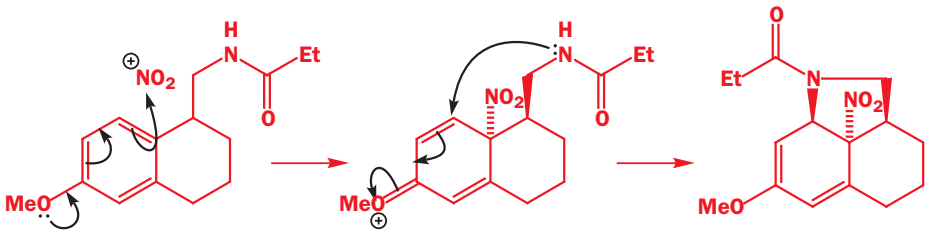
We have hedged this evidence around with caution since the fact that an intermediate can be prepared does not by any means prove that it is involved in a reaction mechanism. In this section we are going to consider other and better evidence for intermediates and at the same time revise some of the earlier material.

Trapping reactions

A more impressive piece of evidence is the design of a molecule that has built into it a functional group that could react with the intermediate in a predictable way but could not reasonably react with other species that might be present. For example, aromatic ethers react with nitrating agents in the *ortho* or *para* positions (Chapter 22). The intermediate has a positive charge delocalized over three of the carbon atoms in the benzene ring. If a nucleophilic group is built into the structure in the right way, it might trap this intermediate and stop it reacting further.



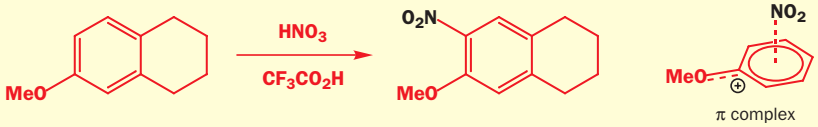
The trapping group is the amide and it has trapped a cation formed by addition of NO_2^+ to the aromatic ring. We are faced with the problem of drawing a mechanism for the formation of this remarkable compound and, when we discover that a necessary intermediate is also an intermediate in our preferred mechanism for aromatic nitration, we feel more confident about that mechanism.



This mechanism explains everything including the stereochemistry. The NO_2^+ attacks the aromatic ring *para* to the OMe group and on the opposite side to the amide. The amide is now in the perfect position to capture the cation at the *meta* position and, because the tether is short, it must form a *cis* bridge.

π complexes in electrophilic aromatic substitution

The weakness in the experiment is that nitration does not occur in that position without the trap but occurs in the *ortho* position. Nevertheless, many chemists believe that aromatic electrophilic substitution actually starts with a loose association of the electrophile with all of the p orbitals of the benzene ring so that here the NO_2^+ group would initially sit at right angles to the plane of the ring in a 'π complex' and would move afterwards to form a σ bond with one particular carbon atom.



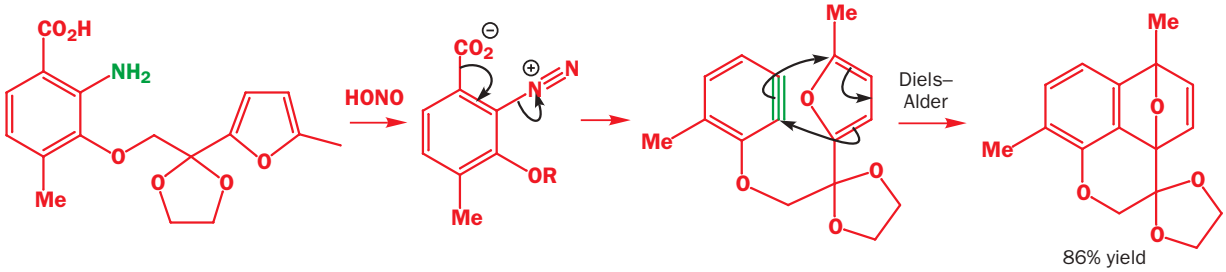
You will meet the related π complexes of metals in Chapter 48.

To be convincing, evidence for an intermediate should include:

- detection of the intermediate in the reaction mixture, perhaps by a trapping reaction
- a demonstration that the intermediate gives the product when added to the reaction mixture (this also means that it must be prepared as an at least reasonably stable compound)
- kinetic evidence that the rate of formation and rate of disappearance are adequate
- other suitable evidence of the kind that we have been discussing in this chapter

What is the cyclic acetal for? It is there to make the cyclization more efficient by the Thorpe–Ingold effect; see Chapter 42.

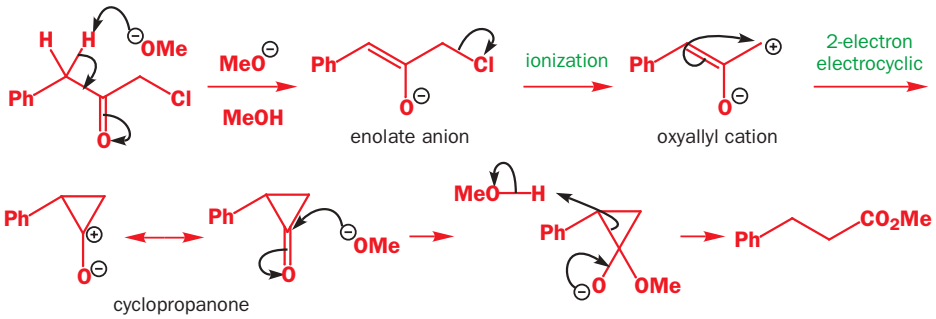
A neat intramolecular trap for benzyne works in this way. A standard benzyne-generating reaction—the diazotization of an *ortho*-amino benzoic acid (Chapter 23) gives a zwitterion that loses nitrogen and CO_2 to release the benzyne. A furan tethered to the next *ortho* position traps the benzyne in an intramolecular Diels–Alder reaction. The yield is impressive and the trap is very efficient.



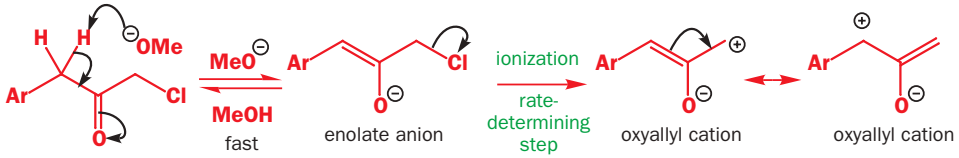
The argument is that this reaction cannot really be explained without a benzyne intermediate. This same method of making benzyne is used on other *o*-amino benzoic acids and so they presumably create benzynes too.

A collection of reactions linked by a common intermediate

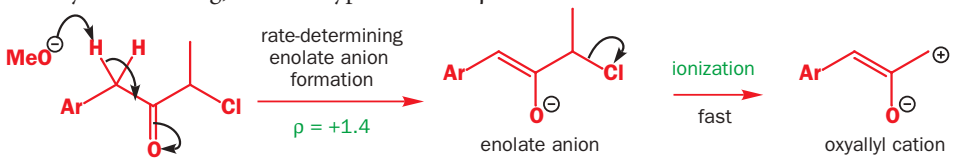
Particularly convincing evidence can develop when a number of chemists suggest the same intermediate for a number of different reactions and show that it is possible to trap the intermediate from one reaction, put it into the others, and get the normal products. We are going to describe one set of such related reactions. In Chapter 37 we suggested a mechanism for the Favorskii rearrangement involving a series of remarkable intermediates. Here is an example.

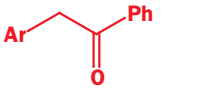


A quick summary of the evidence on this particular example. If the reaction is run in MeOD instead of MeOH, the starting material becomes deuterated at the site of enolate formation suggesting that this is a fast and reversible step. The entropy of activation for the reaction is $\Delta S^{\ddagger}$ = +64 J mol^{-1} K^{-1}, suggesting that the slow step is one molecule breaking into two. There is only one such step—the second, ionization step. If various substituted phenyl groups are used, the Hammett ρ value is –5. This large negative value also suggests that the ionization is the slow step as the cation is delocalized into the benzene ring.

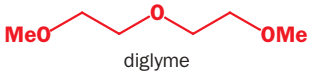


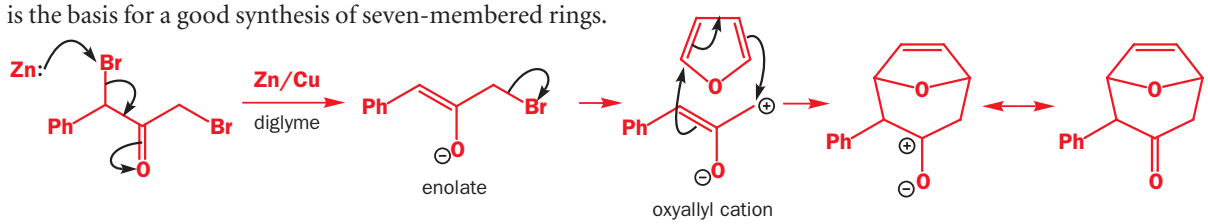
So there is some evidence for the first intermediate—the exchange of deuterium from the solvent. The formation of the enolate can even become the rate-determining step! If we merely add an extra methyl group to the chloroketone the reaction becomes 220 times faster and the rate-determining step changes. There is no longer any exchange of deuterium from the solvent and the Hammett ρ value changes from –5 to +1.4. This small positive value, showing some modest increase in electron density near the ring, matches typical known ρ values for enolate formation.



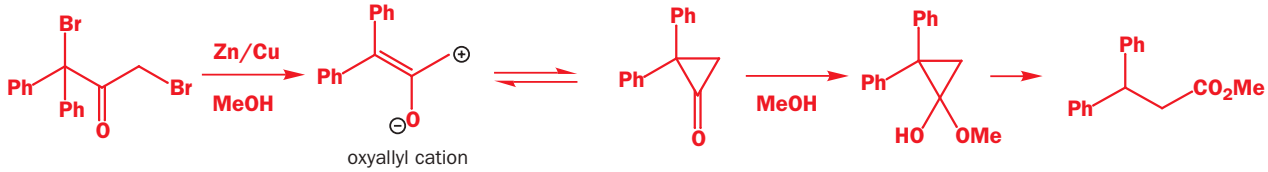


However, we are not surprised that an enolate ion is formed from a ketone in basic solution. The oxyallyl cation is much more surprising. How can we be convinced that it really is an intermediate? There are several alternative ways to make the same intermediate. If basic nucleophiles such as the methoxide ion are avoided and reaction of zinc with an α,α′-dibromoketone in a nonnucleophilic solvent like diglyme is used instead, the oxyallyl cation can be trapped in a Diels–Alder reaction. This is the basis for a good synthesis of seven-membered rings.

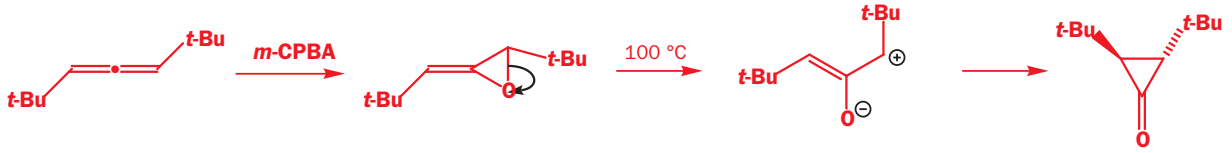




But does the oxyallyl cation go on to give cyclopropanones? In fact, there is good evidence that the two are in equilibrium. If the same method is used to create the diphenyl oxyallyl cation in methanol instead of in diglyme, the normal Favorskii product is produced. Evidently, methoxide is needed only to produce the enolate—methanol is enough to decompose the cyclopropanone.

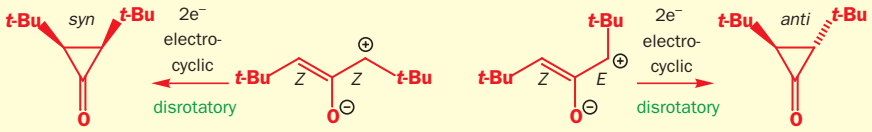


If a suitable (1,3-di-*t*-butyl) allene is epoxidized with *m*-CPBA the unstable allene oxide can actually be isolated. On heating, this epoxide gives a stable *trans*-di-*t*-butylcyclopropanone. It is very difficult to see how this reaction could happen except via the oxyallyl cation intermediate.

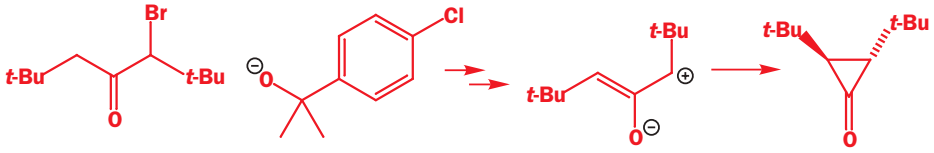


Why draw the oxyallyl cation with this stereochemistry?

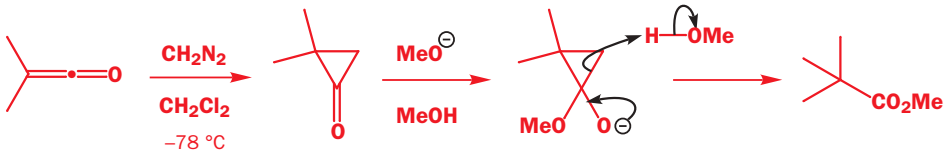
If the closure to the cyclopropanone is electrocyclic then it will be disrotatory (Chapter 36). The *E,Z*-isomer we have drawn gives the *anti* cyclopropanone while either the *E,E*- or the *Z,Z*-oxyallyl cation gives the *syn*-di-*t*-butylcyclopropanone.



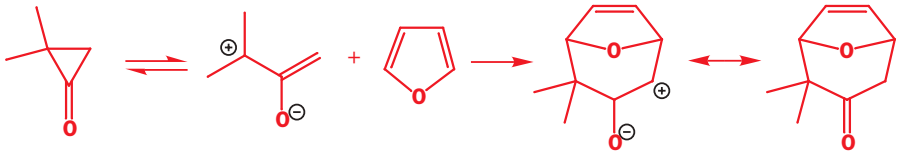
But is the same cyclopropanone an intermediate in the Favorskii reaction? If the bromoketone is treated with methoxide in methanol, it gives the Favorskii product but, if it is treated with a much more hindered base, such as the potassium phenoxide shown, it gives the same cyclopropanone with the same stereochemistry.



Other, less stable cyclopropanones, such as the 2,2-dimethyl compound, can be made by carbene addition (Chapter 40) to ketenes. This compound did the Favorskii reaction with methoxide in methanol: the only product came from the expected loss of the less unstable carbanion. This will, of course, be general-acid-catalysed by methanol as no free carbanion can be released into an alcoholic solvent.



The same cyclopropanone gives a cycloadduct with furans—this must surely be a reaction of the oxyallyl cation and we can conclude that the three isomeric reactive intermediates (allene oxide, cyclopropanone, and oxyallyl cation) are all in equilibrium and give whichever product is appropriate for the conditions.

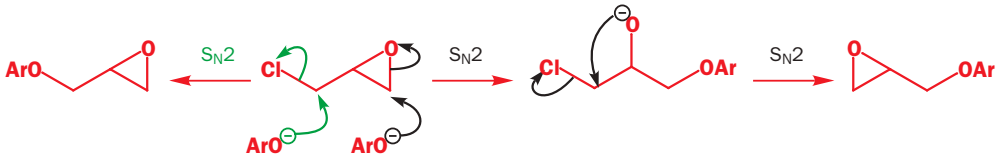


Though it is never possible to prove a mechanism, this interlocking network of intermediates, all known to be formed under the reaction conditions, all being trapped in various ways, and all known to give the products, is very convincing. If any part of the mechanism were not correct, that would throw doubt on all the other reactions as well. Nevertheless, this mechanism is not accepted by all chemists.

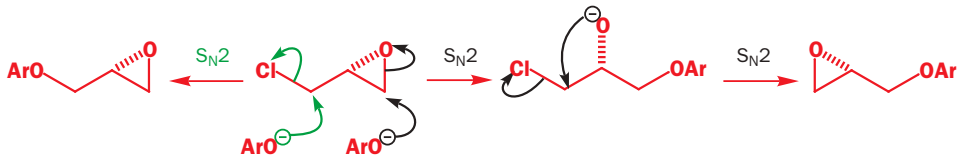
Stereochemistry and mechanism

This chapter ends with a survey of the role of stereochemistry in the determination of mechanism. Though we have left stereochemistry to the last, it is one of the most important tools in unravelling complex mechanisms. You have already seen how inversion of configuration is a vital piece of evidence for an S_N2 mechanism (Chapter 17) while retention of configuration is the best evidence for participation (Chapter 37). You have seen the array of stereochemical evidence for pericyclic mechanisms (Chapters 35 and 36). The chapters devoted to diastereoselectivity (33 and 34) give many examples where the mechanism follows from the stereochemistry. We shall not go over that material again, but summarize the types of evidence with new examples. The first example looks too trivial to mention.

Though this reaction looks like a simple S_N2 displacement by the naphthyloxide anion on the primary alkyl chloride, there is, in fact, a reasonable alternative—the opening of the epoxide at the less hindered primary centre followed by closure of the epoxide the other way round. The electrophile is called 'epichlorohydrin' and has two reasonable sites for nucleophilic attack.

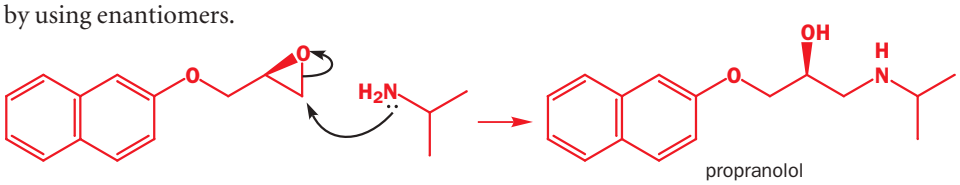


It looks difficult to tell these mechanisms apart since both involve the same kind of reaction. Stereochemistry is the answer. If enantiomerically pure epichlorohydrin is used, the two mechanisms give different enantiomers of the product. Though each S_N2 reaction takes place at a primary centre and the stereogenic centre remains the same, from the diagrams the two products are obviously enantiomers.



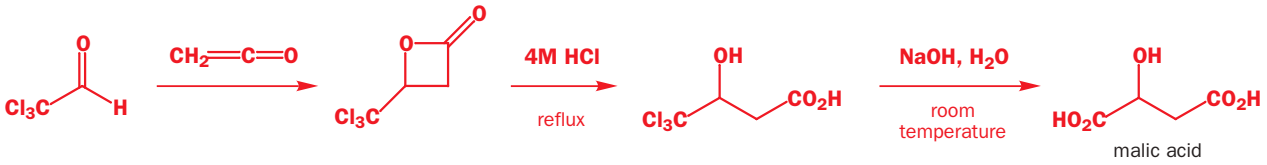
Finding out the mechanism of this process is not idle curiosity as a group of drugs used to combat high blood pressure and heart disease, such as propranolol, are made from epichlorohydrin and it is essential to know which enantiomer to use to get the right enantiomer of the drug. In fact, the more extended mechanism shown in black is correct. This is an example of determination of mechanism by using enantiomers.

■ The full synthesis of propranolol is given in Chapter 30.

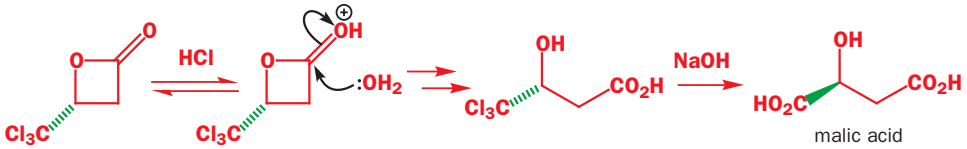


propranolol

A more complicated example arises from the strange reactions used to make malic acid from chloral and ketene. An initial [2 + 2] cycloaddition (Chapter 35) is followed by acid treatment and then treatment with an excess of aqueous NaOH. Neutralization gives malic acid, an acid found naturally in apples (*Malus* spp.).

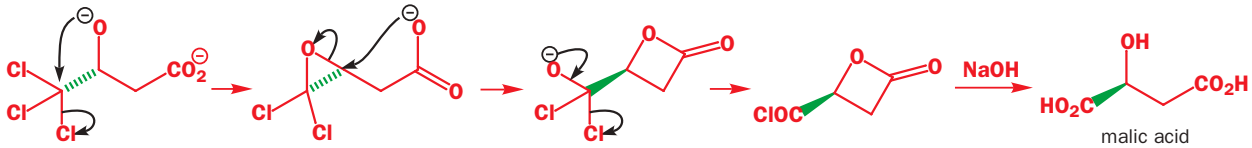


The mechanism of this reaction also looks straightforward: normal ester hydrolysis followed by hydrolysis of the CCl_3 group to CO_2H. Caution suggests investigation, particularly as four-membered lactones sometimes hydrolyse by S_N2 displacement at the saturated ester carbon rather than by attack on the carbonyl group, like the three-membered lactones discussed in Chapter 37 (p. 000). The solution was urgently needed when it was found that enantiomerically pure lactone could be prepared by asymmetric synthesis (Chapter 45). The sequence was repeated with enantiomerically pure lactone: lactone hydrolysis occurred with retention of configuration and must be normal ester hydrolysis by attack of water at the carbonyl group. But the hydrolysis of the CCl_3 group occurred with inversion of configuration.



■ You will see in Chapter 42 that this reaction is governed by 'Baldwin's rules' and why attack on even a CCl_2 group is unfavourable.

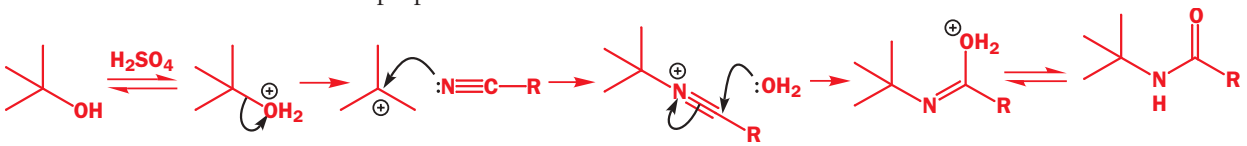
The answer must be a mechanism related to the one we have just seen for epichlorohydrin. Attack by hydroxide on CCl_3 is almost unknown and it is much more likely that intramolecular attack by alkoxide to give an epoxide should occur. The carboxylate anion can then invert the stereogenic centre by intramolecular S_N2 displacement at the central carbon atom. Notice that the tether ensures attack at the central atom. The second four-membered lactone also hydrolyses by attack at the carbonyl group.



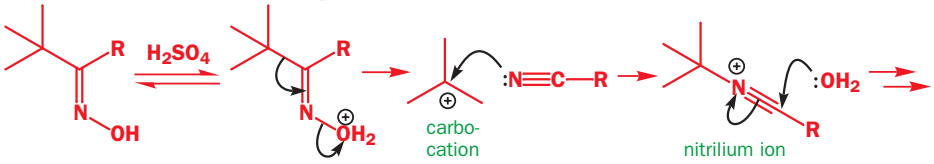
■ The Ritter reaction was introduced in Chapter 17 and the Beckmann fragmentation in Chapter 38.

The Ritter reaction and the Beckmann fragmentation

Another collection of related intermediates occurs in the Ritter reaction and the Beckmann fragmentation. The **Ritter reaction** involves the combination of a tertiary alcohol and a nitrile in acid solution and the proposed mechanism involves a series of intermediates.



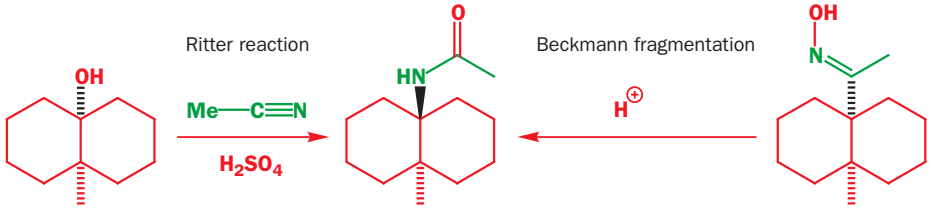
The Beckmann fragmentation also occurs in acid solution upon the fragmentation of an oxime with a *tertiary* alkyl group *anti* to the OH of the oxime. The fragmentation step gives the same cation and the same nitrile together with a molecule of water and these three combine in the same way to give the same amide. We need evidence that the carbocation and the nitrilium ion are genuine intermediates and that the same sequence is found in both reactions.



Evidence that the two reactions are intimately related comes from the formation of the same amide from two different starting materials: a tertiary alcohol and an oxime, both based on the

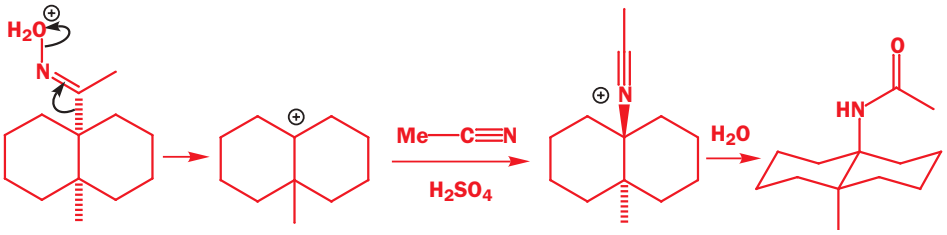
decalin skeleton. The oxime has its OH group *anti* to the ring junction to minimize steric hindrance as oxime formation is under thermodynamic control (Chapter 14).

■ Decalins are widely used in conformational experiments; see Chapter 18.

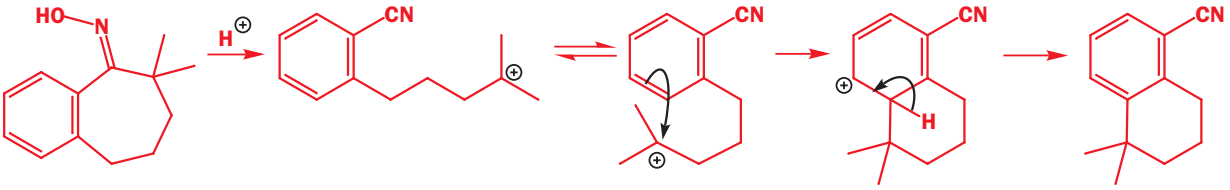


The experiments also provide stereochemical evidence that a carbocation is an intermediate in both reactions. Both starting materials are *cis*-decalins but the product is a *trans*-decalin. The carbocation intermediate has no stereochemistry and can react with the nitrile from either face. Axial attack is preferred and it gives the stable *trans*-decalin. The formation of the carbocation is shown only by the Beckmann fragmentation: formation from the alcohol by the S_N1 mechanism is obvious.

▶ None of these compounds is chiral as there is a plane of symmetry running vertically through each molecule. We are discussing diastereoisomers only.

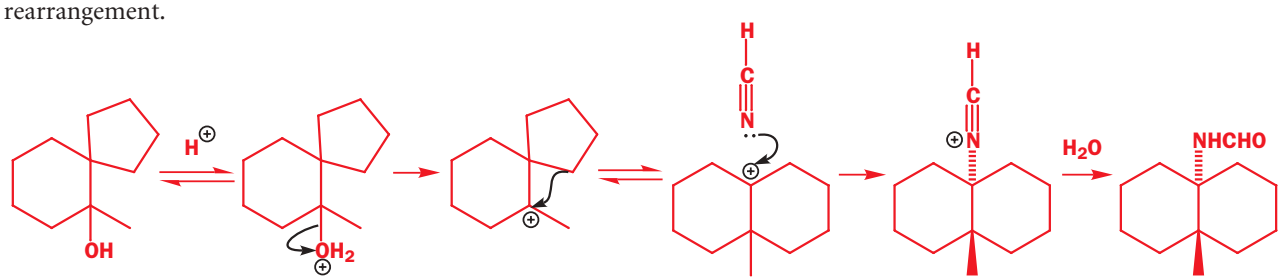


Trapping the carbocation is also possible. The Beckmann fragmentation on this oxime of an aryl seven-membered ring ketone gives a tertiary carbocation that might be expected to cyclize to give an amide. However, this reaction would give an unfavourable eight-membered ring (see Chapter 42) and does not happen. Instead, the chain twists round the other way and forms a much more stable six-membered ring by intramolecular Friedel–Crafts alkylation. Note that the regioselectivity is *meta* to CN and *ortho* to alkyl. These are both favourable but the main factor is the C_4 tether making any other product impossible.



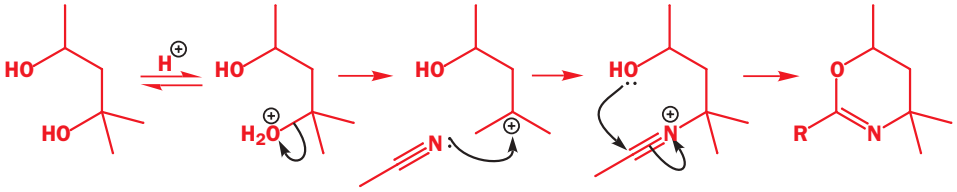
In the Ritter reaction a rather different kind of evidence for the cation is the fact that families of isomeric alcohols all give the same product. In all these cases, rearrangements of the first formed carbocation (Chapter 37) can easily account for the products. Another example in the decalin series is this Ritter reaction with KCN as the nitrile in acidic solution so that HCN is the reagent. The starting material is a spirocyclic tertiary alcohol but the product is a *trans*-decalin formed by rearrangement.

▶ This would be a dangerous experiment to carry out and is not recommended.

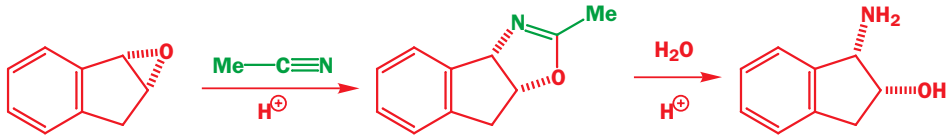


Trapping the nitrilium cation is also possible. The most famous example is probably the heterocycle (an oxazine, Chapter 42) produced by intramolecular capture of the nitrilium ion with a hydrox-

yl group. Note that the tertiary alcohol reacts to give the cation while the secondary alcohol acts as the nucleophilic trap.



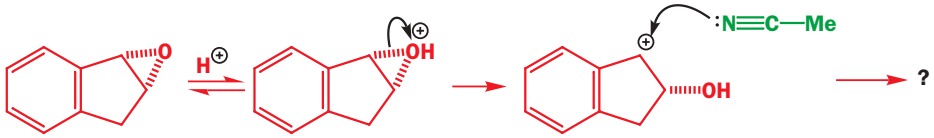
An important example in which the diastereoisomer produced was critical in determining the mechanism is the synthesis of *cis*-aminoindanol, a part of Merck's anti-HIV drug Crixivan (indinavir). The reaction involves treatment of indene epoxide with acetonitrile (MeCN) in acidic solution. The product is a *cis* fused heterocycle. It is easy to see which atoms have come from the nitrile (green) but the substitution of nitrogen for oxygen at one end of the epoxide has occurred with retention of configuration as the *cis*-epoxide has given the *cis* product. Clearly, we have some sort of Ritter reaction and the nitrilium ion has been trapped with an OH group.



indene epoxide

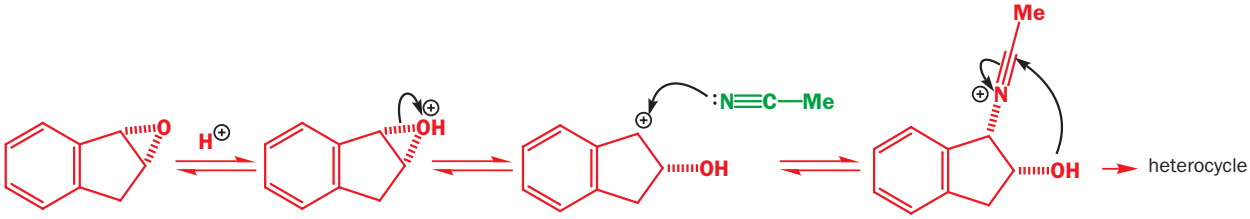
cis-aminoindanol

What about the regioselectivity? The obvious explanation is that a cation is formed from the epoxide in a specific acid-catalysed ring opening. But why should the nitrile attack the bottom face of the cation? We should expect it to attack the top face preferentially as the hydroxyl group partly blocks the bottom face.

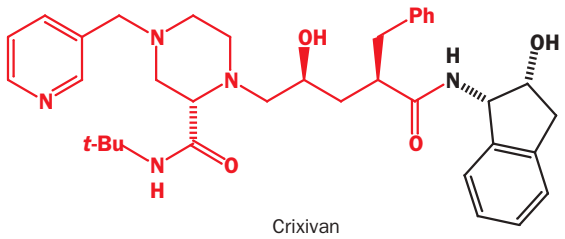


■ This step will be described in Chapter 42 as a favourable '5-*endo*-*dig*' process (p. 000).

A reasonable mechanism is that in which the nitrile adds reversibly to the cation. Every time it adds to the top face, it drops off again as the OH group cannot reach it to form the heterocycle. Every time it adds to the bottom face, it is quickly captured by the OH group because 5/5 fused rings are favourable when the ring junction is *cis*. Eventually, all the compound is converted to the heterocycle.



Again, the mechanism of this reaction is of great importance because it is the foundation stone of the synthesis of Crixivan—a drug that is saving thousands of lives. These last examples are of reactions that you would find difficult to classify into any of the familiar types we have met so far in the book. Nevertheless, the organic chemist needs to be able to propose mechanisms for new reactions and to have a general idea of the methods available to test these proposals.



Crixivan

Summary of methods for the investigation of mechanism

This brief summary is for guidance only and the figures quoted are approximate ranges only. The full text above should be used for detail. All methods would not be used in one investigation.

1. Make sure of the structure of the product

- Basic structure (Chapters 4 and 11) and stereochemistry (Chapter 32) by spectroscopic methods
- Detail of fate of individual atoms by labelling with D, ^{13}C, and ^{18}O. Double labelling may help
- Stereochemical course of the reaction (enantio- or diastereoselectivity) may be critical

2. Kinetic methods

- Rate equation gives composition of main transition state
- Deuterium isotope effect: $k_H > k_D$ shows bond to H formed and/or broken in transition state. Values k_H/k_D 2–7 typical
- Entropy of activation shows increase ($\Delta S^{\ddagger}$ positive) or decrease ($\Delta S^{\ddagger}$ negative) in disorder.Typical values and deductions:
  - $\Delta S^{\ddagger}$ positive (rarely larger than +50 J mol^{-1} K^{-1}): one molecule breaks into two or three
  - Moderate negative values: no change in number of molecules (one goes to one etc.) or bimolecular reaction with solvent
  - Large negative values: two molecules go to one or unimolecular reaction with ordered $TS^{\ddagger}$ (cycloaddition, etc.)

3. Correlation of structure and reactivity

- Replace one group by another of similar size but different electronic demand (CF_3 for CH_3 or OMe for CH_3)
- Systematic Hammett σ/ρ correlation with *m*- and *p*-substituted benzenes:
  - Sign of ρ: +ρ indicates electrons flowing into and –ρ electrons flowing out of ring in transition state
  - Magnitude of ρ shows effect on the benzene ring:

    large (around 5), charge on ring (+ρ, anion; –ρ, cation)

    moderate (around 2–4), charge on atom next to ring—may be gain or loss of conjugation

    small (<1), ring may be distant from scene of action or ρ may be balance of two ρs of opposite sign

4. Catalysis

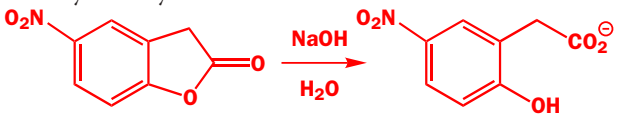
- pH–rate profile reveals specific acid or base catalysis
- Rate variation with [HA] or [B] at constant pH reveals GAC or GBC
- Deuterium isotope effect: normal ($k_H > k_D$) shows GA/BC, inverse solvent $k(D_2O) > k(H_2O)$ shows SA/BC
- GA/BC is termolecular and has large negative entropy of activation

5. Intermediates

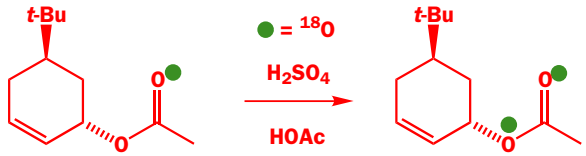
- Independent preparation or, better, isolation from or detection in reaction mixture helps
- Must show that intermediate gives product under reaction conditions
- Designed trapping experiments often most convincing

Problems

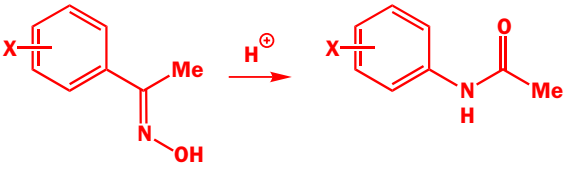
1. Propose three fundamentally different mechanisms (other than variations of the same mechanism with different kinds of catalysis) for this reaction. How would (a) D labelling and (b) ^{18}O labelling help to distinguish the mechanisms? What other experiments would you carry out to eliminate some of these mechanisms?



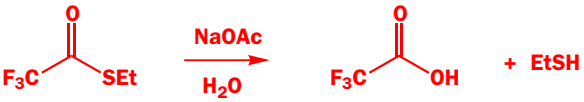
2. Explain the stereochemistry and labelling pattern in this reaction.



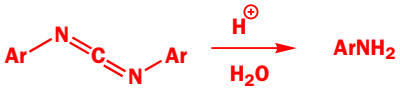
3. The Hammett ρ value for migrating aryl groups in the acid-catalysed Beckmann rearrangement is –2.0. What does this tell us about the rate-determining step?



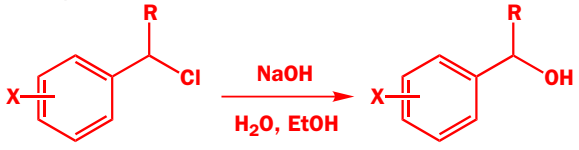
4. Between pH 2 and 7, the rate of hydrolysis of this thiol ester is independent of pH. At pH 5 the rate is proportional to the concentration of acetate ion [AcO^-] in the solution and the reaction goes twice as fast in D_2O as in H_2O. Suggest a mechanism for the pH-independent hydrolysis. Above pH 7, the rate increases with pH. What kind of change is this?



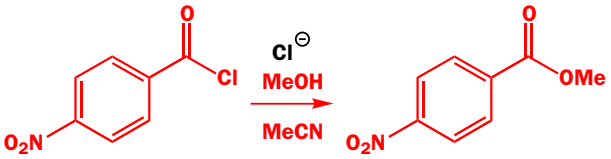
5. In acid solution, the hydrolysis of this carbodiimide has a Hammett ρ value of –0.8. What mechanism might account for this?



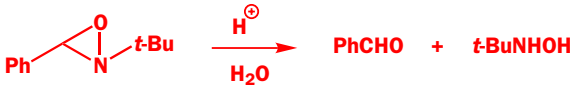
6. Explain the difference between these Hammett ρ values by mechanisms for the two reactions. In both cases the ring marked with the substituent X is varied. When R = H, ρ = –0.3 but, when R = Ph, ρ = –5.1.



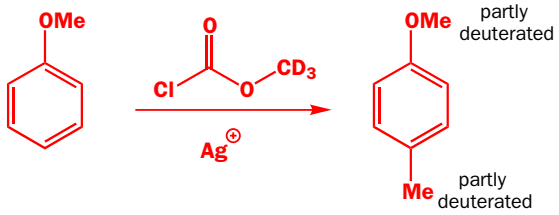
7. Explain how chloride ion catalyses this reaction.



8. The hydrolysis of this oxaziridine in 0.1 M sulfuric acid has $k(H_2O)/k(D_2O) = 0.7$ and an entropy of activation of $\Delta S^{\ddagger} = -76$ J mol^{-1} K^{-1}. Suggest a mechanism for the reaction.

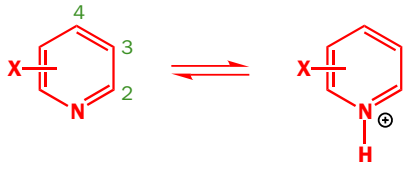


9. Explain how both methyl groups in the product of this reaction come to be labelled. If the starting material is re-isolated at 50% reaction, its methyl group is also labelled.



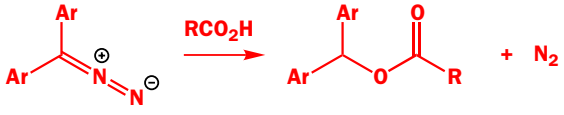
10. The pK_{aH} values of some substituted pyridines are as follows.

X	H	3-Cl	3-Me	4-Me	3-MeO	4-MeO	3-NO_2
pK_{aH}	5.2	2.84	5.68	6.02	4.88	6.62	0.81

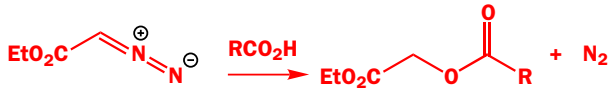


Can the Hammett correlation be applied to pyridines using the σ values for benzenes? What equilibrium ρ value does it give and how do you interpret it? Why are no 2-substituted pyridines included in the list?

11. These two reactions of diazo compounds with carboxylic acids give gaseous nitrogen and esters as products. In both cases the rate of the reaction is proportional to [diazo compound]·[RCO_2H]. Use the data for each reaction to suggest mechanisms and comment on the difference between them.



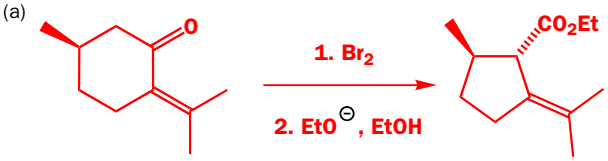
ρ = – 1.6 $k(RCO_2H)/k(RCO_2D)$ = 3.5



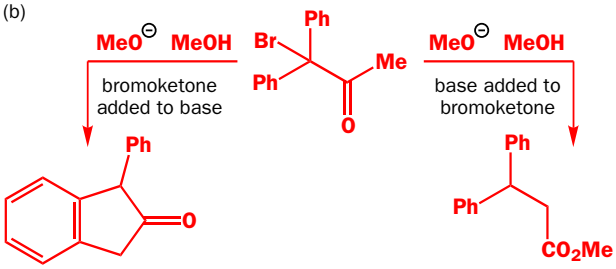
$k(RCO_2D)/k(RCO_2H)$ = 2.9

12. Suggest mechanisms for these reactions and comment on their relevance to the Favorskii family of mechanisms.

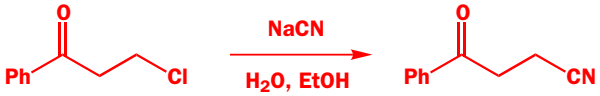
(a)



(b)



13. If you believed that this reaction went by elimination followed by conjugate addition, what experiment would you carry out to try and prove that the enone is an intermediate?



14. This question is about three related acid-catalysed reactions: (**a**) the isomerization of *Z*-cinnamic acids to *E*-cinnamic acids; (**b**) the dehydration of the related hydroxy-acids; (**c**) the racemization of the same hydroxy-acids. You should be able to use the information provided to build up a complete picture of the interaction of the various compounds and the intermediates in the reactions.

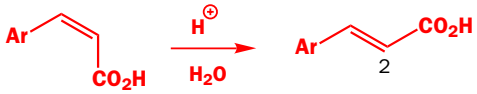
(**a**) Data determined for the acid-catalysed isomerization of *Z*-cinnamic acids in water include the following.

(**i**) The rate is faster in H_2O than in D_2O: $k(H_2O)/k(D_2O) = 2.5$.

(**ii**) The product contains about 80% D at C2.

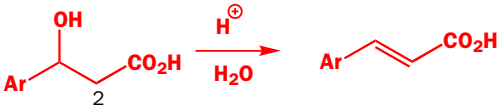
(**iii**) The Hammett ρ value is –5.

Suggest a mechanism for the reaction that explains the data.



(**b**) The dehydration of the related hydroxy-acids also gives *E*-cinnamic acids at a greater rate under the same conditions but the data for the reaction are rather different.

(**i**) Hydroxy-acid deuterated at C2 shows a kinetic isotope effect: $k_H/k_D = 2.5$.



(**c**) If the dehydration reaction is stopped after about 10% conversion to products, the remaining starting material is completely racemized. Data for the *racemization* reaction include the following.

(**i**) The rate is slower in H_2O than in D_2O.

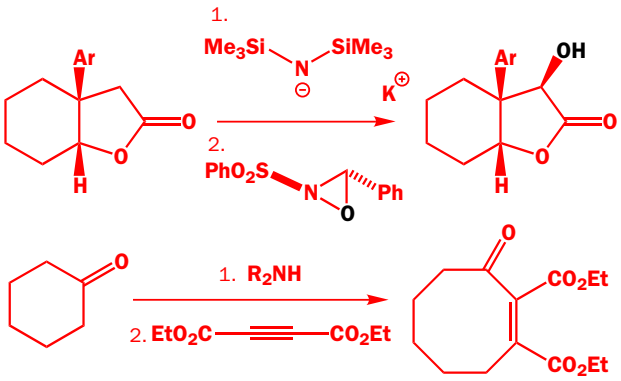
(**ii**) Hydroxy-acid deuterated at C2 shows practically no kinetic isotope effect.

(**iii**) The Hammett ρ value is –4.5.

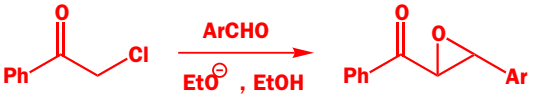
What conclusions can you draw about the dehydration?

Recalling that the dehydration goes faster than the isomerization, what would be present in the reaction mixture if the isomerization were stopped at 50% completion?

15. Propose mechanisms for the two reactions at the start of the chapter. The other product in the first reaction is the imine $PhCH{=}NSO_2Ph$.



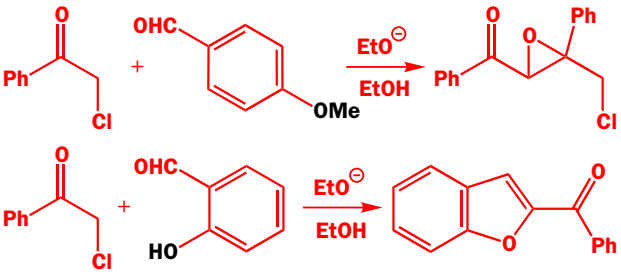
16. A typical Darzens reaction involves the base-catalysed formation of an epoxide from an α-haloketone and an aldehyde. Suggest a mechanism for the Darzens reaction consistent with the results shown below.



(**a**) The rate expression is:
rate = k_3[PhCO·CH_2Cl][ArCHO][EtO^-]

(**b**) When Ar is varied, the Hammett ρ value is +2.5.

(**c**) The following attempted Darzens reactions produced unexpected products.



Saturated heterocycles and stereoelectronics

42

Connections

Building on:

- Acetals and hemiacetals ch14
- Stereochemistry ch16
- The conformation of cyclic molecules ch18
- Stereospecific elimination reactions ch19
- Protecting groups ch24
- NMR and stereochemistry—how orbital overlap affects coupling (the Karplus relationship) ch32
- How rings affect stereoselective reactions ch33
- Ring closing and opening by cycloadditions ch35
- Electrocyclic ring closing and opening ch36
- How alignment of orbitals affects reactivity ch37–ch38
- Determining organic mechanisms ch41

Arriving at:

- Putting a heteroatom in a ring changes the reactivity of the heteroatom
- Ring-opening reactions: the effect of ring strain
- Lone pairs in heterocycles have precise orientations
- Some substituents prefer to be axial on some six-membered saturated heterocycles
- Interactions of lone pairs with empty orbitals can control conformation
- Ring-closing reactions: why five-membered rings form quickly and four-membered rings form slowly
- Baldwin's rules: why some ring closures work well while others don't work at all

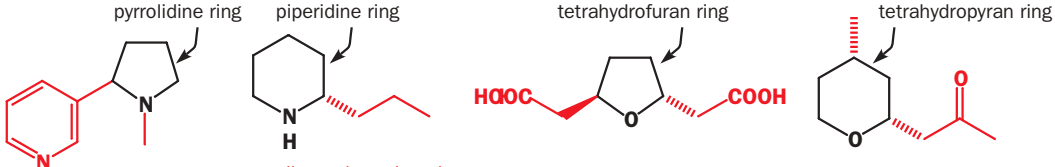
Looking forward to:

- Structure and reactions of aromatic heterocycles ch43
- Synthesis of aromatic heterocycles ch44
- Asymmetric synthesis ch45
- Chemistry of life ch49
- Mechanisms in biological chemistry ch50
- Natural products ch51

Introduction

Rings in molecules make a difference, and we have already devoted the whole of one chapter (33) and most of another (18) just to the structure and reactions of rings. In those chapters, the message was that rings have well-defined conformations, and that well-defined conformations allow reactions to be stereoselective.

This chapter and the next two will revisit the ring theme, but the rings will all be **heterocycles**: rings containing not just carbon atoms, but oxygen, nitrogen, or sulfur as well. It may seem strange that this rather narrowly defined class of compounds deserves three whole chapters, but you will soon see that this is justified both by the sheer number and variety of heterocycles that exist and by their special chemical features. Chapters 43 and 44 cover heterocycles that are aromatic, and in this chapter we look at heterocycles that are saturated and flexible. Some examples, a few of which may be familiar to you, are shown below and overleaf.



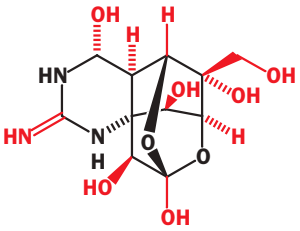
nicotine

coniine – the poison in hemlock that killed Socrates

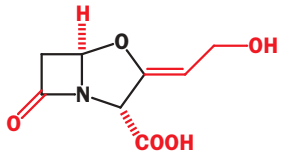
human waste product: 3–5 mg per day excreted in urine

"rose oxide ketone" – isolated from geranium oil and used in the perfume industry

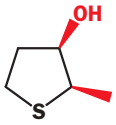
■ The saturated heterocyclic rings are shown in black, and names for the most important ring types are given: some (like piperidine, morpholine) you will need to remember; others (tetrahydrofuran, pyrrolidine) are more obviously derived from the names for aromatic heterocycles that we will discuss in the next chapter. Some of these compounds (nicotine, coniine, cocaine) are plant products falling into the class called alkaloids. Alkaloids are discussed in Chapter 51. Another important class of saturated heterocycles, sugars, will reappear in Chapter 49.



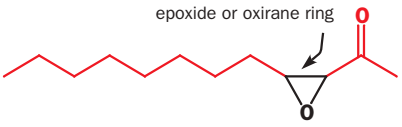
tetrodotoxin – lethal poison in wrongly prepared and cooked Japanese puffer fish



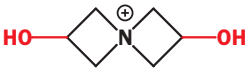
clavulanic acid – an antibiotic



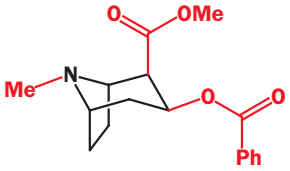
musty taste of "corked" wine



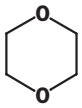
sex pheromone of the Grey Duiker antelope



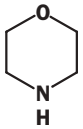
isolated from the green alga *Chara globularis*



cocaine



dioxane: a common solvent



morpholine: an important base

■ In Chapters 35 and 36 we discussed pericyclic ring closing and opening (cycloadditions and electrocyclic reactions) that are subject to the Woodward–Hoffmann rules of orbital symmetry. This chapter will be looking at ring closing and opening by the simple addition, substitution, and elimination reactions: orbital symmetry is not an issue in saturated systems, but orbital *shape* and *orientation* is.

But what are the 'special chemical features' of saturated heterocycles? Putting a heteroatom into a ring does two important things, and these lead to the most important new topics in this chapter. Firstly, the heteroatom makes the ring easy to make by a ring-closing reaction, or (in some cases) easy to break by a ring-opening reaction. Closing and opening reactions of rings are subject to constraints that you will need to know about, and the principles that govern these reactions are discussed in the second half of the chapter.

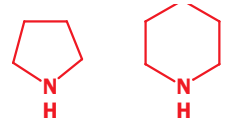
Secondly, the ring fixes the orientation of the heteroatom—and, in particular, the orientation of its lone pairs—relative to the atoms around it. This has consequences for the reactivity and conformation of the heterocycle which can be explained using the concept of **stereoelectronics**.

● **Stereoelectronic effects are chemical consequences of the arrangement of orbitals in space.**

Although this is the only chapter in which stereoelectronics appears in the title, you will soon recognize the similarity between the ideas we cover here and concepts like the stereospecificity of E2 elimination reactions (Chapter 19), the Karplus relationship (Chapter 32), the Felkin–Anh transition state (Chapter 33), and the conformational requirements for rearrangement (Chapter 37) and fragmentation (Chapter 38) reactions.

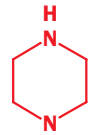
Reactions of heterocycles

Nitrogen heterocycles: amines, but more nucleophilic

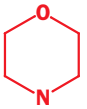


pyrrolidine

piperidine

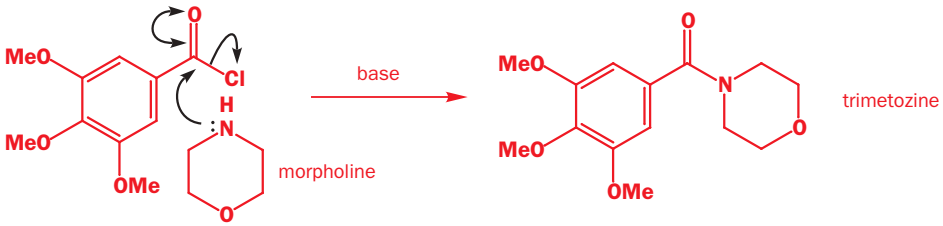


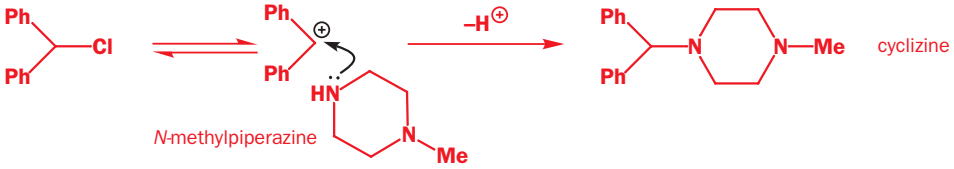
piperazine



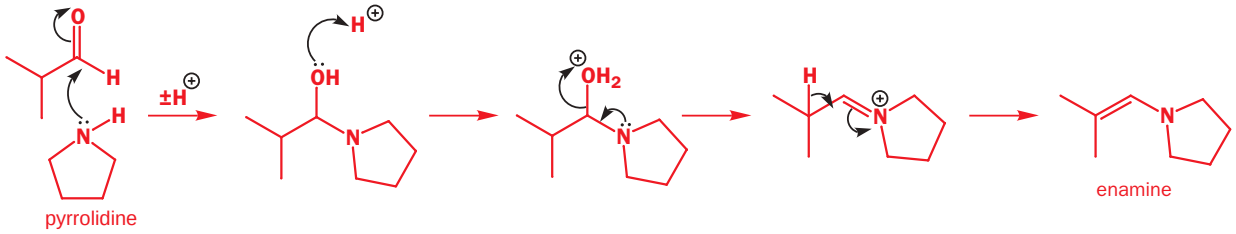
morpholine

In many reactions the simple saturated nitrogen heterocycles—piperidine, pyrrolidine, piperazine, and morpholine—behave simply as secondary amines that happen to be cyclic. They do the sorts of things that other amines do, acting as nucleophiles in addition and substitution reactions. Morpholine, for example, is acylated by 3,4,5-trimethoxybenzoyl chloride to form the tranquillizer and muscle relaxant trimetozine, and *N*-methylpiperazine can be alkylated in an S_N1 reaction with diphenylmethyl chloride to give the travel-sickness drug cyclizine.



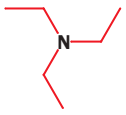
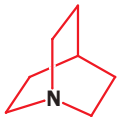
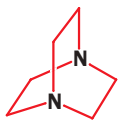


The addition of pyrrolidine to aldehydes and ketones is a particularly important reaction because it leads to enamines, the valuable enol equivalents discussed in Chapter 26.



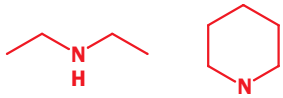
Enamines formed from pyrrolidine and piperidine are particularly stable, because pyrrolidine and piperidine are rather more nucleophilic than comparable acylic amines such as diethylamine. This is a general feature of cyclic amines (and cyclic ethers, too, as you will see shortly), and is a steric effect. The alkyl substituents, being tied back into a ring, are held clear of the nucleophilic lone pair, allowing it to approach an electrophile without hindrance. This effect is well illustrated by comparing the rates of reaction of methyl iodide with three amines—tertiary this time. The two cyclic compounds are bridged—quinuclidine is a bridged piperidine while the diamine known as 'DABCO' (1,4-DiAzaBiCyclo[2.2.2]Octane) is a bridged piperazine. Table 42.1 shows the relative rates, along with pK_{aH} values, for triethylamine, quinuclidine, and DABCO.

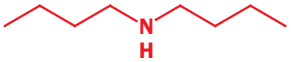
Table 42.1 Rates of reaction of amines with methyl iodide

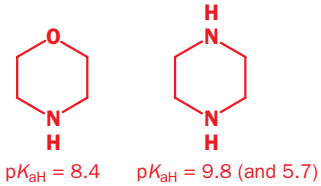
	 triethylamine	 quinuclidine	 DABCO
relative rate of reaction[a]	1	63	40
pK_{aH}	10.7	11.0	8.8 (and 3.0)

[a] Relative rate of reaction with MeI in MeCN at 20 °C.

Quinuclidine and DABCO are 40–60 times more reactive than triethylamine. This is again due to the way the ring structures keep the nitrogen's substituents away from interfering with the lone pair as it attacks the electrophile. You should contrast the effect that the cyclic structure has on the pK_{aH} of the amines: none! Triethylamine and quinuclidine are equally basic and, as you can see in the margin, so (more or less) are diethylamine, dibutylamine, and piperidine. A proton is so small that it cares very little whether the alkyl groups are tied back or not.





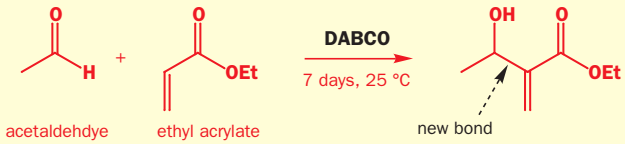


Much more important in determining pK_{aH} is how electron-rich the nitrogen is, and this is the cause of the glaring discrepancy between the basicity of quinuclidine and that of DABCO, or between the basicities of piperidine (pK_{aH} 11.2) and morpholine (pK_{aH} 9.8) or piperazine (pK_{aH} 8.4). The extra heteroatom, through an inductive effect, withdraws electron density from the nitrogen atom, making it less nucleophilic and less basic. In this

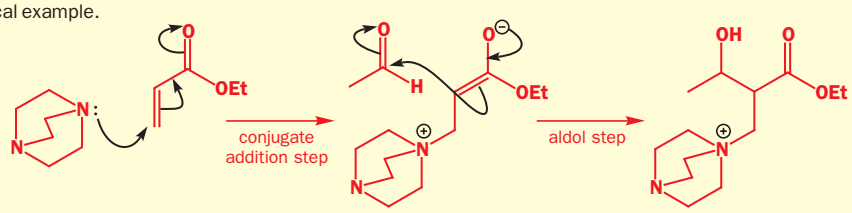
sense, morpholine can be a very useful base, less basic than triethylamine but somewhat more so than pyridine (pK_{aH} 5.2). Notice how much lower is the second pK_{aH} (that is, the pK_{aH} for protonation of the second nitrogen) of the diamines DABCO and piperazine: the protonated nitrogen of the monoprotonated amine withdraws electrons very effectively from the unprotonated one.

The Baylis–Hillman reaction

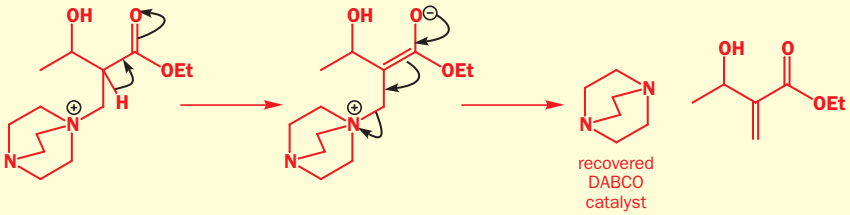
One of the most important uses of DABCO is in the **Baylis–Hillman reaction**, discovered in 1972 by two chemists at the Celanese Corporation in New York. Their reaction is a modification of the aldol reaction (Chapter 27), except that, instead of the enolate being formed by deprotonation, it is formed by conjugate addition. You have seen the enolate products of conjugate addition being trapped by alkylating agents in Chapter 26, but in the Baylis–Hillman reaction, the electrophile is an aldehyde and is present right from the start of the reaction, which is done just by stirring the components at room temperature. Here is a typical example.



The reaction starts with the (relatively nucleophilic) DABCO undergoing conjugate addition to ethyl acrylate. This will form an enolate that can then attack the acetaldehyde in an aldol reaction.

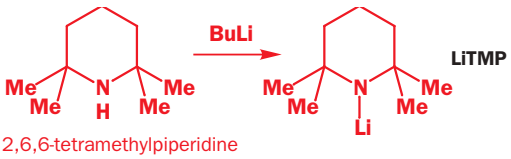


E1cB eliminations often follow aldol reactions and lead to α,β-unsaturated products. In this case, though, DABCO is a much better leaving group than the hydroxyl group, so enolization leads to loss of DABCO in an E1cB elimination, giving the product of the reaction. DABCO is recovered unchanged, and is a catalyst.

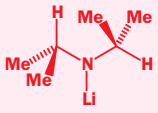


A disadvantage of the Baylis–Hillman reaction is its rate: typically, several days' reaction time are required. Pressure helps speed the reaction up, but as a catalyst DABCO is about the best. It is nucleophilic, because of the 'tied back' alkyl groups, but importantly it is a good leaving group because it has a relatively low pK_a, meaning that it leaves easily in the last step. As you have seen before, good nucleophiles are usually bad leaving groups, though there are many exceptions. DABCO's combination of nucleophilicity and leaving group ability is perfect here.

The exposed nature of the nitrogen atom in cyclic amines means that nitrogen heterocycles are very frequently encountered in drug molecules, particularly those operating on the central nervous system (cocaine, heroin, and morphine all contain nitrogen heterocycles, as do codeine and many tranquillizers such as Valium). But the ring can also be used as a support for adding substituents that hinder the nitrogen's lone pair. Just as the nitrogen atom of piperidine is permanently exposed, the nitrogen atom of 2,2,6,6-tetramethylpiperidine (TMP) nestles deep in a bed of methyl groups. The lithium salt of TMP (LiTMP) is an analogue of LDA—a base that experiences enormous steric hindrance that can be used in situations where the selectivity even of LDA fails.

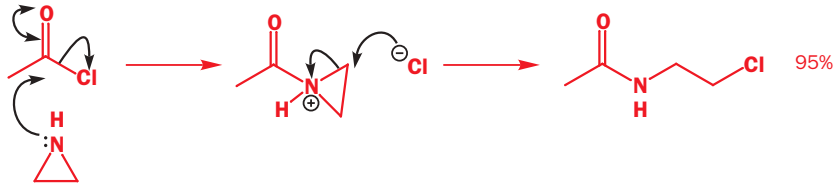


▶ With LDA, one or other of the isopropyl groups always has the option of rotating to place only a C–H group close to the N–Li bond. In LiTMP, there are always four Me groups close to Li.



Aziridine: ring strain promotes ring opening

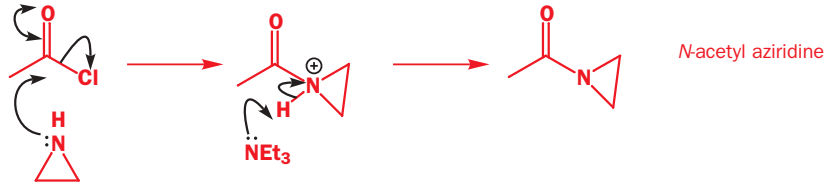
Aziridine and azetidine are stable, if volatile, members of the saturated nitrogen heterocycle family, and aziridine has some interesting chemistry of its own. Like pyrrolidine and piperidine, aziridine can be acylated by treatment with an acyl chloride, but the product is not stable. The ring opens with attack of chloride, a relatively poor nucleophile, and an open-chain secondary amide results.



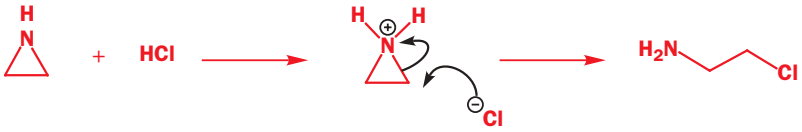
Saturated heterocycles and systematic nomenclature

The names aziridine and azetidine are derived from a reasonably logical system of nomenclature, which assigns three-part heterocycle names according to: (a) the heteroatom ('az-' = nitrogen, 'ox-' = oxygen, 'thi-' = sulfur); (b) the ring size ('-ir-' = 3, from tri; '-et-' = 4, from tetra; '-ol-' = 5; nothing for 6; '-ep-' = 7, from hepta; '-oc-' = 8, from octa; etc.); and (c) the degree of saturation ('-ene' or '-ine' for unsaturated, '-idine' or '-ane' for saturated). Hence az-ir-idine, az-et-idine, di-ox-ol-ane, and ox-ir-ane.

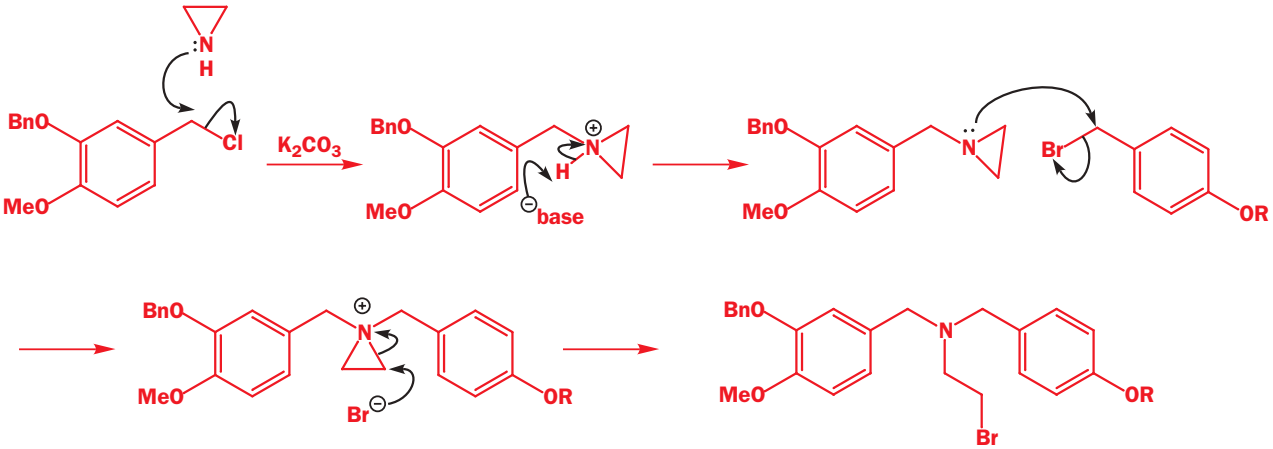
You can view this ring opening as very similar to the ring opening of an epoxide (Chapter 20)—in particular, a *protonated* epoxide, in which the oxygen bears a positive charge. The positive charge is very important for aziridine opening because, when the reaction is done in the presence of a base, removal of the proton leads immediately to the neutral acyl aziridine, which *is* stable.



The ring opening of aziridine is a useful way of making larger heterocycles: anything that puts a positive charge on nitrogen encourages the opening by making N a better leaving group, whether it's protonation, as shown below, or alkylation.



Alkylation of aziridine in base gives the *N*-substituted aziridine as you might expect, but a second alkylation leads to a positively charged aziridinium salt that opens immediately to the useful bromoamine. In this case, the product is an intermediate in the synthesis of two natural products, sandaverine and corgoine.

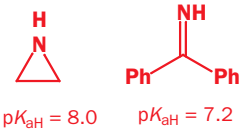


We have just mentioned the protonation of aziridine, and you might imagine from what we said earlier about the comparative nucleophilicity and basicity of nitrogen heterocycles and their acyclic counterparts that aziridine will be even more nucleophilic than pyrrolidine, and about as basic. Well,

■ For a reminder of the terms associated with ring size, look at Chapter 18, p. 000.

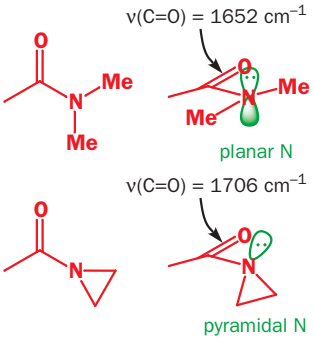
it isn't. The idea that 'tying back' the alkyl groups increases nucleophilicity is only valid for 'normal-sized' (five- or six-membered) rings: with small rings another effect takes over.

Aziridine is, in fact, much less basic than pyrrolidine and piperidine: its pK_{aH} is only 8.0. This is much closer to the pK_{aH} of a compound containing an sp^2 hybridized nitrogen atom—the imine in the margin, for example. This is because the nitrogen's lone pair is in an orbital with much more s character than is typical for an amine, due to the three-membered ring. This is an effect we have discussed before, in Chapter 15, and you should re-read pp. 000–000 if you need to refresh your memory. There we compared three-membered rings with alkynes, explaining that both could be deprotonated relatively easily. The anion carries a negative charge in a low-energy orbital with much s character: the same type of orbital carries aziridine's lone pair.



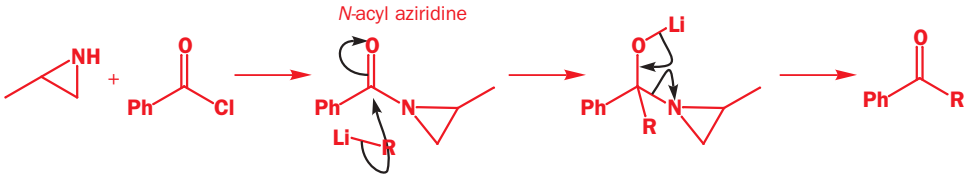
▶ In Chapter 15 we summarized the effect by saying 'Small rings introduce more p character inside the ring and more s character outside it'. Put simply, we can say that, as bond angles decrease, as they must in small rings, the bonds within the ring take up more p character (p orbitals are at an angle of 90° to one another), leaving the bonds (or lone pairs) outside the ring with more s character.

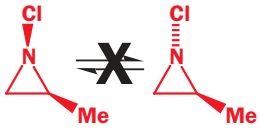
The s character of the aziridine nitrogen's lone pair has other effects too. The lone pair interacts very poorly with an adjacent carbonyl group, so *N*-acyl aziridines such as the one you saw on p. 000 behave not at all like amides. The nitrogen atom is pyramidal and not planar, and the stretching frequency of the C=O bond (1706 cm^{-1}) is much closer to that of a ketone (1710 cm^{-1}) than that of an amide (1650 cm^{-1}).



Lack of conjugation leads to increased reactivity, and *N*-acyl aziridines are useful in synthesis because they react with organolithium reagents only once to give ketones. No further reactions of the product ketone occur because the *N*-acyl aziridine is reactive enough to compete with it for the organolithium reagent.

■ *N*-acyl aziridines therefore behave like Weinreb amides (see p. 000), and stabilization of the tetrahedral intermediate by chelation may also play a role. Esters, of course, typically react twice with organolithiums to give tertiary alcohols.



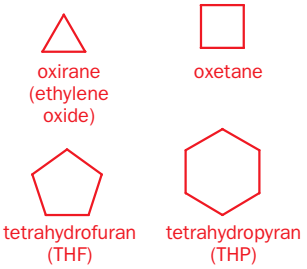


The s character of the lone pair means that the nitrogen atom inverts very slowly, rather like a phosphine (which also carries its lone pair in an s orbital: see Chapter 4, p. 000). Usually it is not possible for nitrogen to be a stereogenic centre because inversion is too rapid—the transition state for nitrogen inversions (in which the lone pair is in a p orbital) is low in energy. But with an aziridine, getting the lone pair into a p orbital would require an awful lot of energy, so nitrogen can be stereogenic and, for example, these two stereoisomers of an *N*-substituted aziridine can be separated and isolated.

Oxygen heterocycles

Ring-opening chemistry is characteristic of oxygen heterocycles too, and there is no need for us to revisit epoxide opening here. Epoxides are particularly reactive because ring opening releases ring strain, driving the reaction forward. However, we can tell you about some chemistry of the most important simple oxygen heterocycle, THF. You may be surprised that THF does any real chemistry: after all, the very reason it is used as a solvent is precisely because it is so unreactive. Oxygen heterocycles are cyclic ethers, and ethers are the least reactive of all the common functional groups.

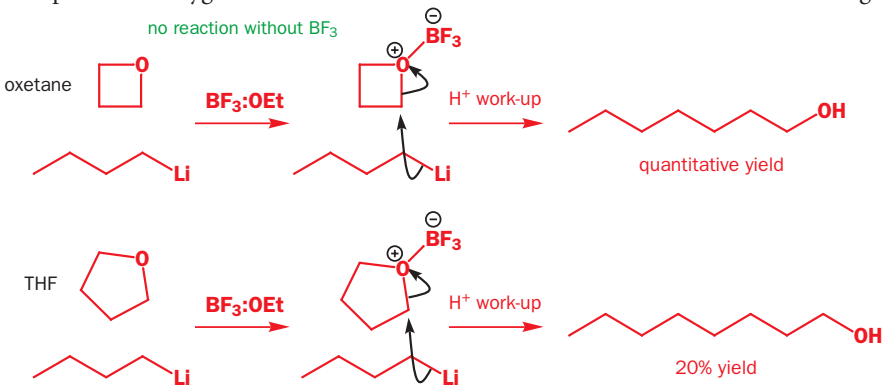
■ Epoxide opening under acidic and basic conditions was covered in Chapter 20.



■ You have seen (Chapters 17 and 23) the use of HBr, BBr_3, and Me_3SiCl to deprotect methyl and benzyl ethers of phenols.

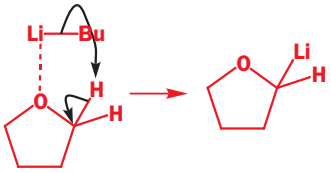
To make ethers more reactive, they must be complexed with strong Lewis acids. BF_3 is commonly used with cyclic ethers, and even with epoxides it increases the rate and yield of the reaction when organometallic reagents are used as nucleophiles. BF_3 is most easily handled as its complex with diethyl ether, written BF_3:OEt. BuLi does not react with oxetane, for example, unless a Lewis acid, such as BF_3, is added, when it opens the four-membered ring to give a quantitative yield of *n*-heptanol.

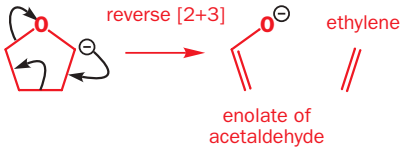
The same reaction happens with THF, but only in much lower yield. Nonetheless, just as cyclic amines are more nucleophilic than acyclic ones, so cyclic ethers are more nucleophilic than acyclic ones. This is one of the reasons why THF is such a good solvent for organolithiums—the nucleophilic lone pair of the oxygen atom stabilizes the electron-deficient lithium atom of the organolithium.



▶ $F_3B^{\ominus}—O^{\oplus}Et_2$ BF_3:OEt_2
Ways of writing BF_3 complex with Et_2O. The oxygen lone pair is donated into the boron's empty p orbital.

A more important reaction between BuLi and THF is not nucleophilic attack, but deprotonation. You will have noticed that reactions involving BuLi in THF are invariably carried out at temperatures of 0 °C or below—usually –78 °C. This is because, at temperatures above 0 °C, deprotonation of THF begins to take place. You might think that this would not be a problem, if BuLi were being used as a base, because the deprotonated THF could still itself act as a base. The trouble is that deprotonated THF is unstable, and it undergoes a reverse [2+3] cycloaddition. Here is the mechanism (we have represented the organolithium as an anion to help with the arrows). The products are: (1) the (much less basic) enolate of acetaldehyde and (2) ethylene. The first tends to polymerize, and the second usually evaporates from the reaction mixture.

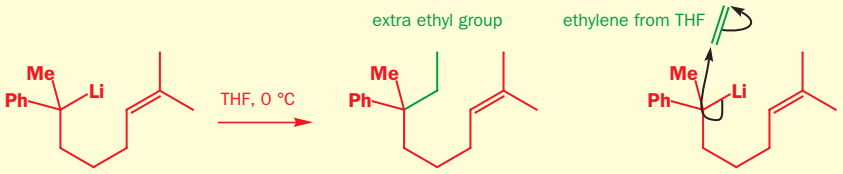




▶ The half-life of *n*-BuLi in THF (in the presence of TMEDA) is 40 min at 20 °C, 5.5 h at 0 °C, and 2 days at –20 °C. Diethyl ether is much less readily deprotonated: at 20 °C in ether *n*-BuLi has a half-life of 10 h. With more basic organolithiums, the rate of decomposition of THF is even faster, and *t*-BuLi can be used in THF only at –78 °C. At –20 °C *t*-BuLi has a half-life in THF of only 45 min; in ether its half-life at this temperature is 7.5 h.

The case of the extra ethyl group

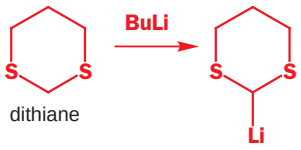
Some chemists in Belgium were studying the reactions of the organolithium shown here to find out whether the anionic centre would attack the double bond to form a five-membered ring (like a radical would: see Chapter 39). The reaction was slow, and they stirred the organolithium in THF for 6 hours at 0 °C. When they worked the reaction up they found no five-membered ring products: instead they got a compound with an extra ethyl group attached! They showed that this ethyl group, in fact, comes from THF: the organolithium did not add to the double bond in the same molecule, but it did add slowly and in low yield to the double bond of the ethylene that is formed by decomposition of THF.



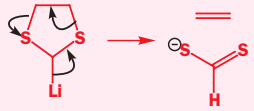
The most common use of tetrahydropyran derivatives is as protecting groups: you met this in Chapter 24 and you can see an example later in the chapter, on p. 000.

Sulfur heterocycles

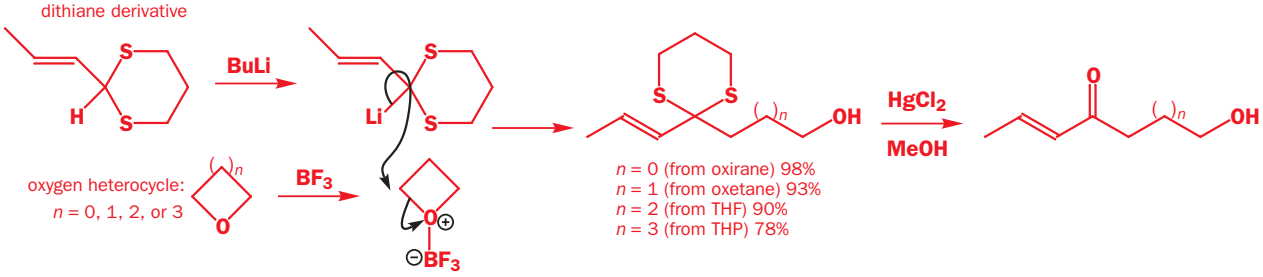
The ability of sulfur to stabilize an adjacent anion will be discussed in Chapter 46, and it means that sulfur heterocycles are much easier to deprotonate than THF. The most important of these contains two sulfur atoms: dithiane. Deprotonation of dithiane occurs in between the two heteroatoms, and you can see some chemistry that arises from this on p. 000. For the moment, we will just show you series of reactions that illustrate nicely both dithiane chemistry and the ring opening of oxygen heterocycles in the presence of BF_3. This substituted derivative of dithiane is deprotonated by BuLi in the same way to give a nucleophilic organolithium that will



▶ Dithiolane, the five-membered version of dithiane, cannot be used in this reaction because, although it is easy to deprotonate, once deprotonated it decomposes by the same mechanism as that used by lithiated THF.



attack electrophiles—even oxygen heterocycles—provided BF_3 is present. The products are formed in excellent yield, even when the electrophile is THP, with no ring strain to drive the reaction. After the addition reaction the dithiane ring can be hydrolysed with mercury(II) (see Chapters 46 and 50 for an explanation) to give a ketone carrying other useful functional groups.



■ The dithiane functions here as an **acyl anion equivalent**. For more on this read Chapter 46.

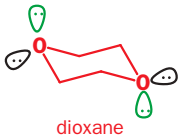
Conformation of saturated heterocycles: the anomeric effect

Heteroatoms in rings have axial and equatorial lone pairs

To a first approximation, the conformation of five- and six-membered saturated heterocycles follows very much the same principles as the conformation of carbocyclic compounds that we detailed in Chapter 18. If you feel you need to re-read the parts of that chapter dealing with rings—chairs and boats, or axial and equatorial substituents—now would be a good time to do it. Sticking with dithiane for the moment, then, this is the conformation. Since the sulfur atoms have lone pairs, they too occupy axial and equatorial positions. The same is true of dioxane or of piperidine.

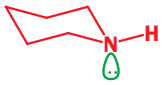
equatorial lone pairs in black

dithiane



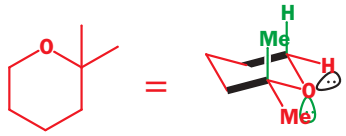
dioxane

axial lone pairs in green



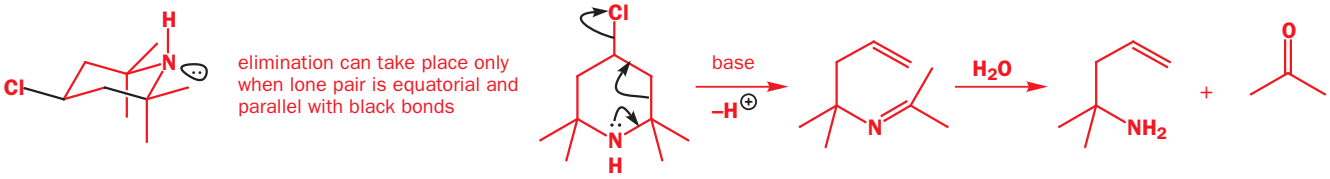
piperidine

We have coloured the lone pairs green or black according to whether they are axial or equatorial, but you can also consider the colour coding in a different way: black lone pairs are parallel with C–C or C–heteroatom bonds in the ring; green lone pairs are parallel with axial C–H bonds outside the ring, or, if the ring has substituents, with the bonds to those substituents. This substituted tetrahydropyran illustrates all this. Notice that the equatorial substituents next to the heteroatom are parallel with neither the green nor the black lone pair.

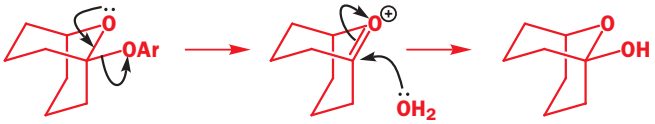


green lone pair parallel with bonds to axial substituents
black lone pair parallel with C–C bonds within ring

Why is this important? Well, if you cast your mind back to Chapter 38, you will remember that the overlap of parallel orbitals was very important in fragmentation reactions. Here, for example, is a fragmentation reaction that goes very well, but that can take place only if the nitrogen's lone pair is equatorial, because only an equatorial (black) lone pair can overlap with the antibonding orbital of the C–C bond that breaks. The chloride leaving group must be equatorial as well.

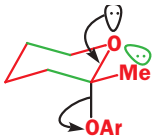


This is not a problem in this example, because flipping of the ring and inversion of the nitrogen are fast, and enough of the starting material is in this conformation at any one time for the reaction to take place. But compare this bicyclic acetal whose 'fragmentation' (actually just an acetal hydrolysis) looks possible by this mechanism.

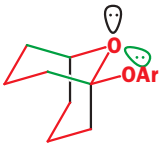


Yet when we try and draw the conformation of the lone pairs we run into a problem: neither over-

laps with the C–O bond that is breaking and so neither can donate its electron density into the C–O σ*. (Another way of looking at this is to say that the intermediate oxonium ion—with a C=O double bond formed by one of the oxygen's lone pairs—would be extremely strained.) Not surprisingly, the rate of hydrolysis of this acetal is extremely slow compared with similar ones in which overlap between the oxygen lone pair and the C–O σ* is possible. The acetal in the margin hydrolyses about 10^{10} times faster.



very fast hydrolysis



neither lone pair overlaps with bond to leaving group

Other situations you have met where overlap between parallel orbitals is important are:

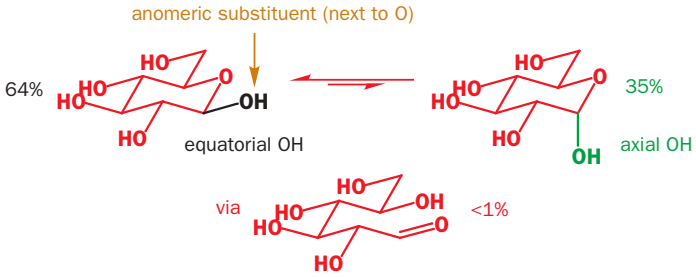
- E2 elimination reactions (Chapter 19)
- NMR coupling constants (Chapter 32)
- reactions of cyclic molecules (Chapter 33)
- the Felkin–Anh transition state conformation (Chapter 34)

Together, these effects are called **stereoelectronic effects**, because they depend on the shape and orientation of orbitals. Most of the examples we have presented you with have been stereoelectronic effects on reactivity, but the next section will deal with how stereoelectronic effects affect **conformation**.

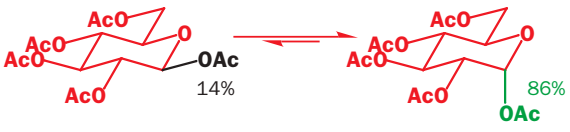
Some substituents of saturated heterocycles prefer to be axial: the anomeric effect

■ We introduced the hemiacetal structure of glucose in Chapter 6, p. 000.

Some of the most important saturated oxygen heterocycles are the sugars. Glucose is a cyclic hemiacetal—a pentasubstituted tetrahydropyran if you like—whose major conformation in solution is shown on the right. About two-thirds of glucose in solution exists as this stereoisomer, but hemiacetal formation and cleavage is rapid, and this is in equilibrium with a further one-third that carries the hemiacetal hydroxyl group axial (<1% is in the open-chain form).



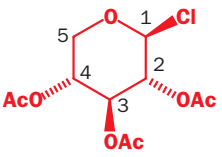
Having read Chapter 18 you will not be surprised that glucose prefers all its substituents to be equatorial. For four of them, of course, there is no choice: they are either all-equatorial or all-axial, and the only way they can get from one to the other is by ring-flipping. But for the fifth substituent, the hydroxyl group next to the ring oxygen (known as the **anomeric** hydroxyl), the choice of axial or equatorial is made available by hemiacetal cleavage and re-formation—it can invert its **configuration**. What is perhaps surprising is that the equatorial preference of this hydroxyl group is so small—only 2:1. Even more surprising is that, for most derivatives of glucose, the anomeric substituents *prefer* to be axial rather than equatorial.



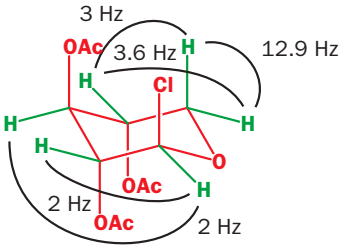
Move away from glucose, and the effect is still there. Here, for example, is the NMR spectrum of this chloro compound. There are now only two possible conformations (no configurational changes are possible because this is not a hemiacetal)—both shown—and from the NMR spectrum you should be able to work out which one this compound has.

δ			*J*, Hz	
5.78	1H	t	2.0	H1
5.03	2H	m		H2, H3
4.86	1H	m		H4
4.37	1H	dd	12.9, 3.0	H5a
3.75	1H	ddd	12.9, 3.7, 0.6	H5b
2.10	9H	s		OAc × 3

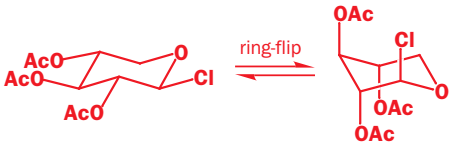
■ NMR in rings was discussed in Chapter 32: this example should come as revision of that material.



The key point is that axial–axial couplings are large (>8 Hz, say), even with adjacent electronegative atoms (which do tend to lower coupling constants). So if H1

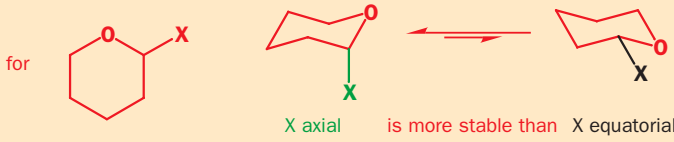


were an axial proton, you would expect it to have a large coupling to H2. But it doesn't—it couples to H2 with J of only 2.0 Hz. (The other coupling is a W-coupling to H3, also of 2.0 Hz: see p. 000.) Similarly, we know that the 12.9 Hz coupling shared by the two H5 protons must be a geminal (^2J) coupling. One of H5a or H5b must be axial; yet both couple to H4 with $J < 4$ Hz. So H4 cannot be axial. With this evidence, we have to conclude that H1 and H4 (and therefore H2 and H3) are equatorial, so the compound must exist mainly in the all-axial conformation. (The 0.6 Hz coupling to H5b is another W-coupling, and shows that H5b is the equatorial proton, and H5a therefore the axial one.)

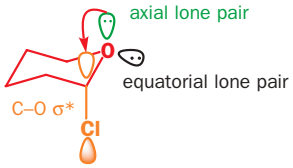


The anomeric effect

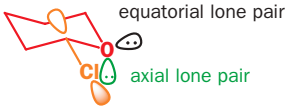
In general, any tetrahydropyran bearing an electronegative substituent in the 2-position will prefer that substituent to be axial. This is is known as the anomeric effect.



But why? This goes against all of what we said in Chapter 18 about axial substituents being more hindered, making conformations carrying axial substituents disfavoured. The key again is stereoelectronics, and we can now link up with the message we left you with at the end of the last section: eliminations and fragmentations can work only when the orbitals involved are parallel.



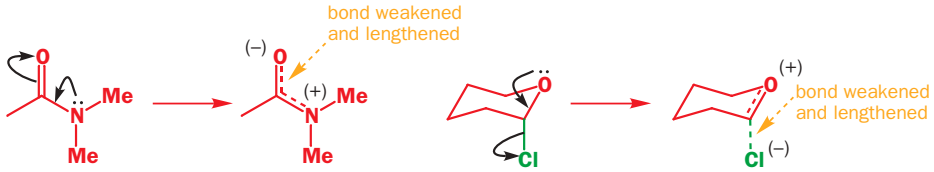
An amide is more stable (less reactive) than a ketone because the p orbital of the N and the low-lying C=O π* of the carbonyl can lie parallel—they can overlap and electron density can move from nitrogen into the C=O bond, weakening C=O. (Evidence for this comes from the lower IR stretching frequency of an amide C=O, among other things.) But C–X bonds also have low-lying antibonding orbitals—the C–X σ*—so we would expect a molecule to be stabilized if an adjacent heteroatom could donate electrons into this orbital in the same way. Take the generalized tetrahydropyran in the box above, for example, with X = Cl, say. This molecule is most stable if an oxygen lone pair can overlap with C–Cl σ*, like this.



incorrectly aligned for overlap with either lone pair

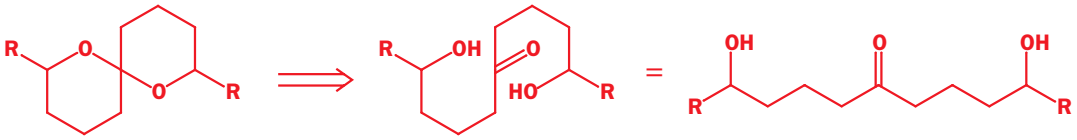
But it can do this only if the chlorine is axial! Remember what we pointed out earlier: the oxygen's equatorial lone pairs are parallel with nothing but bonds in the ring, so the oxygen's axial lone pair is the only one that can help stabilize the molecule, and it can only do this when the Cl is axial. Only the axial conformation benefits from the stabilization, and this is the origin of the anomeric effect.

How shall we represent the stabilization? Comparing again with the amide stabilization, you might think about how to represent it with curly arrows: this is straightforward with the amide and you have seen it many times. But it looks odd with our heterocycle: electron density moves from O to Cl, and the C–Cl bond is weakened. If the process carried right on, Cl^- would leave. This is exactly what did happen in the acetal we presented you with as an example on p. 000: only the axial OAr could leave, however, because of the same requirement for overlap with an oxygen lone pair. In the real structure that we are now looking at, the Cl is still there: the C–Cl bond is weaker, and some of the oxygen's electron density is delocalized on to Cl. This can be seen in crystal structures: compounds exhibiting an anomeric effect have a longer (and therefore weakened) bond outside the ring and a shorter, stronger C–O bond within the ring.



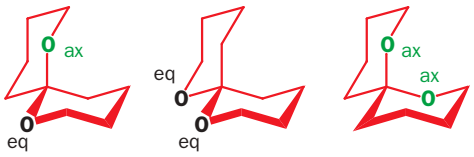
The anomeric effect in some other compounds

Now that you know about the anomeric effect, you should add it to your mental array of ways of explaining 'unexpected' results. Here is an example. Many fruit flies have pheromones based around a 'spiroketal' structure, which we could represent without stereochemistry as shown below. You can imagine the spiroketal (that is, an acetal of a ketone made of two rings joined at a single atom) being made from a dihydroxyketone—and, indeed, this is very often how they are made synthetically. But this is a bad representation because these compounds do have stereochemistry, and the stereochemistry is very interesting.



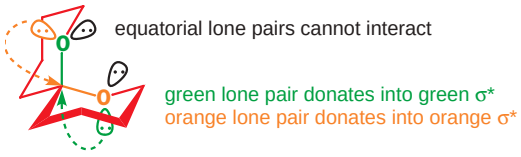
spiroketal structure of some insect pheromones

Let's start with the simplest example, with R = H (a pheromone of the olive fly). Once you have drawn one ring in its chair conformation, there are three ways of attaching the other ring, shown here. If you think they all look the same, consider the orientation of each C–O bond with respect to the ring that it is not part of: you can have each C–O axial or equatorial, and there are three possible arrangements (three conformations).

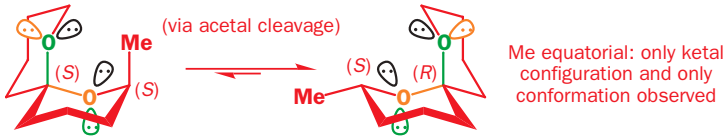


▶ This is a chiral compound, even though the acetal centre is not a chiral centre: no conformation has a plane of symmetry.

Without knowing about the anomeric effect, you would find it hard to predict which conformation is favoured, and, indeed, you might expect to get a mixture of all three. But NMR tells us that this compound exists entirely in one conformation: the last one here, in which each oxygen is axial on the other ring. Only in this conformation can both C–O bonds benefit from the anomeric effect—this is often known as the **double anomeric effect**.

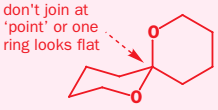


Things become even more interesting when the spiroketal carries substituents. The pheromone of *Epeolus crucifer* , for example, carries one additional methyl group at a centre with (*S*) configuration. The spiroketal centre is now a chiral centre, and also exists in a single configuration. Only one possible conformation allows the methyl substituent to be equatorial and the two oxygens to be axial, and that conformation defines the configuration at the spiroketal. Only one diastereoisomer is formed, in which the methyl group controls the *spiro* centre.



Me equatorial: only ketal configuration and only conformation observed

▶ If you try to draw these spirocyclic acetals you will soon find there is a trick to getting them to look right: the *spiro* carbon has to be one of the four that aren't at the 'point' of either ring; otherwise one ring ends up looking flat.

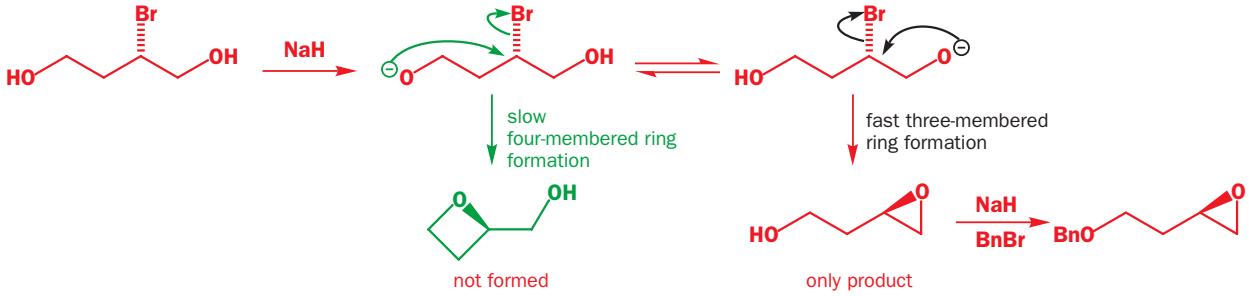


UNHELPFUL REPRESENTATION

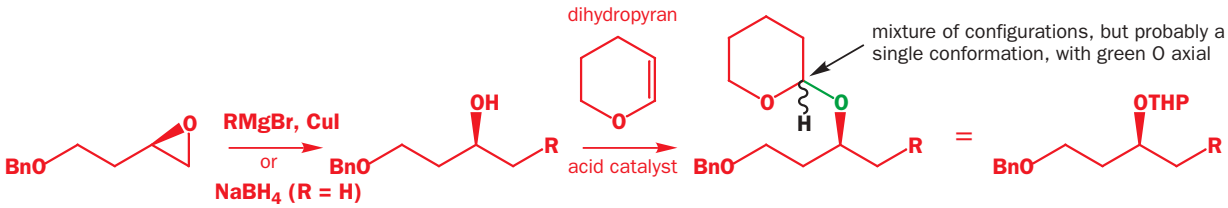
The fact that the substituents on the side chains can control the conformation of the spiroketal centre means that it is not necessary to worry about that centre in a synthesis, provided you are trying to make the spiroketal that has the double anomeric stabilization (both oxygens axial) and that has any substituents equatorial on the rings. A recent (1997) synthesis of a single enantiomer of some fruit-fly pheromones from an aspartic acid-derived bromodiol is shown overleaf. It involves three different-sized oxygen heterocycles.

The diol is made into an epoxide by an intramolecular substitution reaction that is S_N2 and so goes with inversion. There are two possible rings that could form, depending on which hydroxyl group attacks, but (as you will shortly see) three-membered rings form faster than four-membered ones, and the reaction gives none of the oxetane. The other hydroxyl group can now be protected as a benzyl ether.

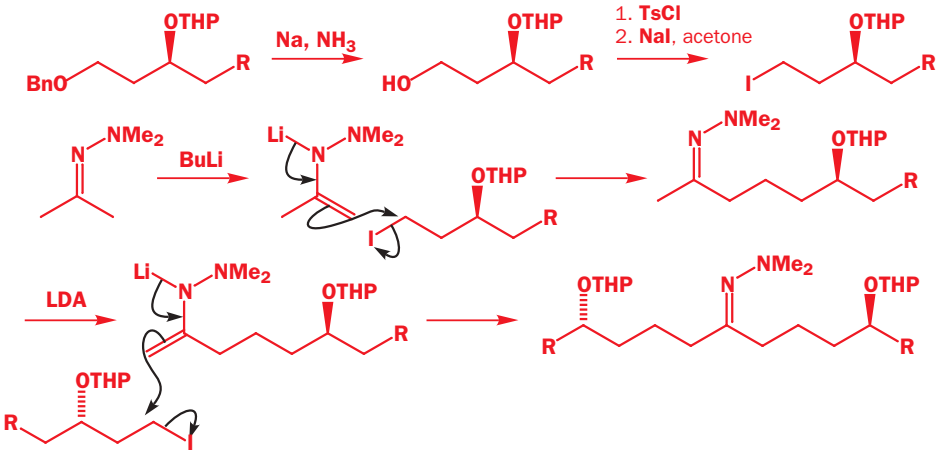
■ There is more on asymmetric synthesis, including some pheromone examples, in Chapter 45. The protecting groups used in this synthesis were covered in Chapter 24, and aza-enolate alkylations in Chapter 26.



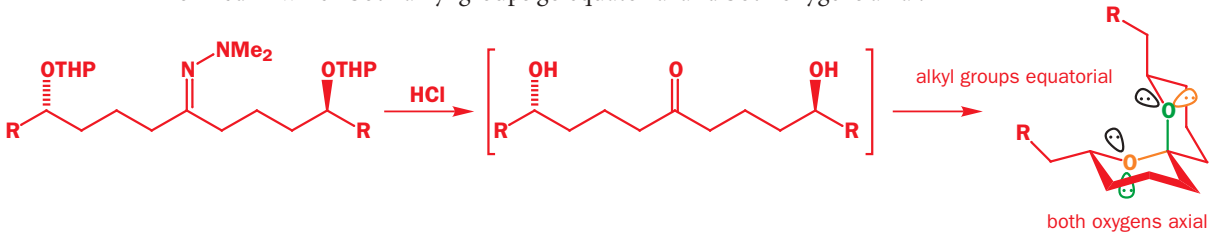
The epoxide opens well with either a copper derivative (RMgBr + CuI) or simply $NaBH_4$, and the resulting alcohol needs to be protected. A good, and in this instance topical, choice is a THP group, added using dihydropyran in the presence of acid. The disadvantage of THP protecting groups is that they introduce an unwanted chiral centre: this will not be controlled and we expect a mixture of both (*R*) and (*S*) configurations at this centre. However, you should now have no problem predicting the *conformation* of the THP rings, even if it is irrelevant to the synthesis.



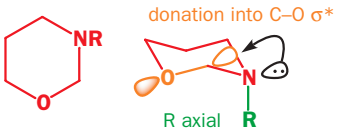
Now the benzyl ether can be deprotected, and the hydroxyl group substituted for iodide via its tosylate. This iodide is an alkylating agent, and is used for two successive alkylations of a hydrazone's aza-enolate.



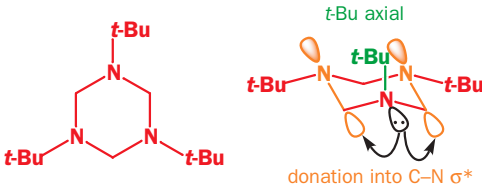
The product is still a hydrazone, and it needs hydrolysing to the ketone with 1 M HCl. These conditions cause immediate hydrolysis of the THP protecting groups and then cyclization to the spiroacetal, which forms with complete control over stereochemistry— a single diastereoisomer is formed in which both alkyl groups go equatorial and both oxygens axial.



Remember that the key requirement for the anomeric effect is that there is a heteroatom with a lone pair (O, N, S usually) adjacent to (that is, in a position to interact with) a low-lying antibonding orbital—usually a C–X σ* (where X = halogen or O). The C–X bond doesn't have to be within the ring—for example, this nitrogen heterocycle prefers to have the R group axial so that the nitrogen gets an equatorial lone pair. Equatorial lone pairs are parallel with bonds within the ring, one of which is C–O, and this conformation is therefore stabilized by an N lone pair/C–O σ* interaction.



It would be a bit much for this 1,3,5-triazine to have all three *t*-butyl groups axial (too much steric hindrance), but it can get away with having one of them axial, benefiting from the resulting equatorial lone pair, which can overlap with two C–N σ*s in the ring.

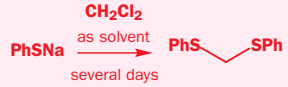


Related effects in other types of compounds

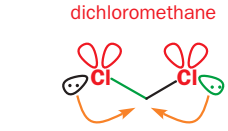
Any conformation in which a lone pair is anti-periplanar to a low-energy antibonding orbital will be stabilized by a stereoelectronic interaction.

As you will probably realize, it's not only in six-membered rings that stereoelectronic interactions between filled and unfilled orbitals stabilize some conformations more than others. Stereoelectronic effects control the conformations of many types of molecules. We shall look at three common compounds that are stabilized by stereoelectronic effects: in two cases, the stabilization is specific to one conformation, and we can use stereoelectronics to explain what would otherwise be an unexpected result.

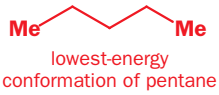
▶ Dichloromethane will react as an electrophile, but it needs a very powerful nucleophile and long reaction times.



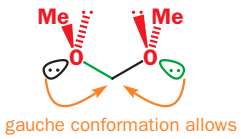
But we start with a compound that is so simple that it has only one conformation because it has no rotatable bonds: dichloromethane. You may have wondered why it is that, while methyl chloride (chloromethane) is a reactive electrophile that takes part readily in substitution reactions, dichloromethane is so unreactive that it can be used as a solvent in which substitution reactions of other alkyl halides take place. You may think that this is a steric effect: indeed, Cl is bigger than H. But CH_2Cl_2 is much less reactive as an electrophile than ethyl chloride or propyl chloride: there must be more to its unreactivity. And there is: dichloromethane benefits from a sort of 'permanent anomeric effect'. One lone pair of each chlorine is always anti-periplanar to the other C–Cl bond so that there is always stabilization from this effect.



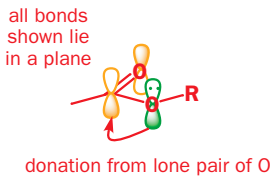
Among the most widespread classes of acyclic compounds to exhibit stereoelectronic control over conformation are acetals. Take the simple acetal of formaldehyde and methanol, for example: what is its conformation? An obvious suggestion is to draw it fully extended so that every group is fully anti-periplanar to every other—this would be the lowest-energy conformation of pentane, which you get if you just replace the Os with CH_2s.



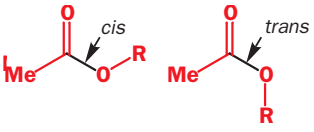
The trouble is, in this conformation none of the oxygen lone pairs get the chance to donate into the C–O σ* orbitals. Although putting the bonds anti-periplanar to one another makes steric sense, electronically, the molecule much prefers to put the lone pairs anti-periplanar to the C–O bonds, so the bonds themselves end up gauche (synclinal) to one another. This is known as the **gauche effect**, but is really just another way in which the stereoelectronic effects that give rise to the anomeric effect turn up in acyclic systems.



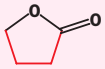
Finally, an even more familiar example that you may never have thought about. You are well aware now that amides are planar, with partially double C–N bonds, and that tertiary amides have one alkyl group *cis* to oxygen and one *trans*. But what about esters? Esters are less reactive than acyl chlorides because of donation from the oxygen p orbital into the carbonyl π*, so we expect them to be planar too, and they are. But there are two possible planar conformations for an ester: one with R *cis* to oxygen and one with R *trans*. Which is preferred?



■ We discussed this in relation to DMF in Chapter 00, p. 000.



▶ Some esters—lactones, for example—cannot lie *cis* for steric reasons, and this is one of the reasons why lactones are distinctly more reactive than esters and in many reactions behave more like ketones: lactones are quite easy to reduce with $NaBH_4$, for example.



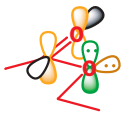
trans arrangement enforced by ring

Here are the two conformations drawn out for ethyl acetate. When the ethyl group (= R) and O are *cis*, not only can one oxygen lone pair interact with the C=O π*, but the other lone pair can also donate into the σ* of the C=O bond. This is not possible when Et and O are *trans*: they are no longer anti-periplanar. The *cis* conformation of esters is generally the preferred one, even in formate esters, where the alkyl group ends up in what is clearly a more sterically hindered orientation.

cis about C–O

in this conformation, additional stabilization is possible as second lone pair of O donates into C–O σ*

trans about C–O

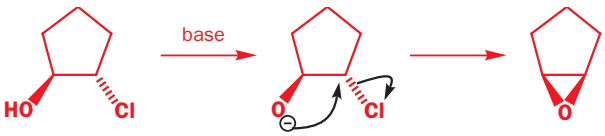


in this conformation, no additional stabilization is possible. Second lone pair of O cannot donate into C–O σ*

Making heterocycles: ring-closing reactions

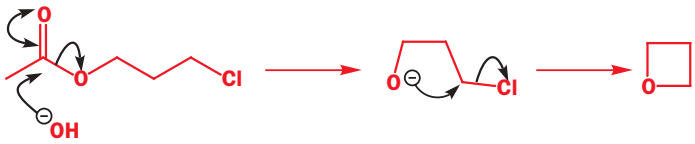
We have talked about the structure of saturated heterocycles, particularly with regard to stereoelectronic control over conformation, and before that we looked at some of their reactions. In this last section of the chapter we will look at how to make saturated heterocycles. By far the most important way of making them is by **ring-closing reactions**, because we can usually use the heteroatom as the nucleophile in an intramolecular substitution or addition reaction. Ring-closing reactions are, of course, just the opposite of the ring-opening reactions we talked about earlier in the chapter, and we can start with a reaction that works well in both directions: ring closure to form an epoxide. You know well that epoxides can be formed using *m*-CPBA and an alkene, but you have already seen examples (including one earlier in the chapter) where they form by an intramolecular substitution reaction such as this.

■ *m*-CPBA epoxidation is discussed in Chapters 19 and 33. In Chapter 33 we explained how ring opening of epoxides joined to six-membered rings was controlled by conformational factors: that discussion relates closely to what we will say here.

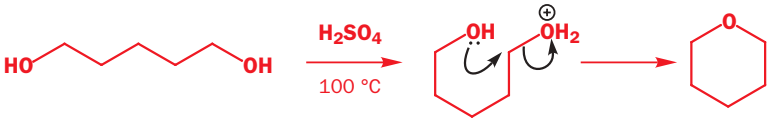


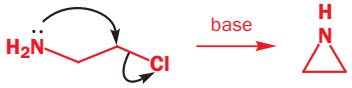
The same method can also be used to generate larger cyclic ethers. Oxetane, for example, is conveniently made by adding 3-chloropropyl acetate to hot potassium hydroxide.

The first step in this reaction is the hydrolysis of the ester. The alkoxide produced then undergoes an intramolecular substitution reaction to yield oxetane.



Tetrahydropyran was prepared as early as 1890 by a ring closure that occurs when a mixture of 1,5-pentanediol with sulfuric acid is heated.



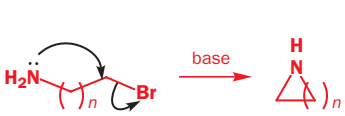


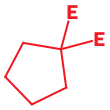
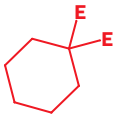
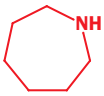
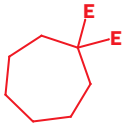
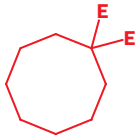
These are all S_N2 reactions, so you will not be surprised that nitrogen heterocycles can be prepared in the same way. Aziridine itself, for example, was first prepared in 1888 from 2-chloroethylamine.

This method works well to form three-, five-, and six-membered nitrogen heterocycles, but does not work well to form four-membered rings. In fact, four-membered rings are generally among the

hardest of all to form. To illustrate this, the first two columns of Table 42.2 show the rates (relative to six-membered ring formation = 1) at which bromoamines of various chain lengths cyclize to saturated nitrogen heterocycles of three to seven members.

Table 42.2 Rates of ring-closing reactions



Ring size	Product	Relative rate[a]	Product[b]	Relative rate[a]	Assessment of rate
3		0.07			moderate
4		0.001		0.58	slow
5		100		833	very fast
6		1		1	fast
7		0.002		0.0087	slow
8				0.00015	very slow

[a] Relative to the six-membered ring formation (= 1).

[b] E = CO_2Et.

The first thing that strikes you perhaps is that the figures in the third column have been produced by a random number generator! There seems to be no rhyme or reason to them, and no consistent trend. To convince you that these numbers mean something, Table 42.2 also shows, in its next two columns, the relative rates for a quite different ring-closing reaction, this time forming four- to seven-membered rings that are not even heterocycles by intramolecular alkylation of a substituted malonate. Though the numbers are quite different in the two cases, the ups and downs are the same, and the final column summarizes the relative rates. Put another way, a rough guide (only rough!—it doesn't work in all cases) to the rate of ring formation is this.

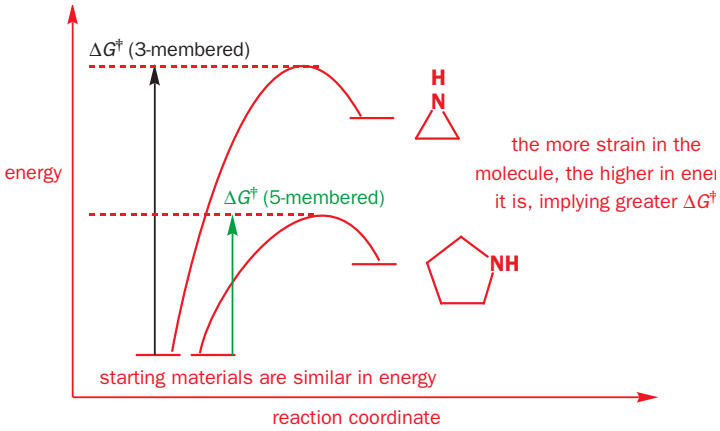
Rough guide to the rate of formation of saturated rings

5 > 6 > 3 > 7 > 4 > 8–10

■ Remind yourself of our definition of small, normal, medium, and large rings, and what ring strain means, by re-reading p. 000. We will deal with what happens in large rings a little later.

We show the numbers in colour to highlight the fact that this seemingly illogical ordering of numbers actually conceals two superimposed trends. Once you get to five-membered rings, the rate of formation drops consistently as the ring size moves from 'normal' to 'medium'. 'Small' (three- and four-membered) rings insert into the sequence below six.

The reason for the two superimposed trends is two opposing factors. Firstly, small rings form slowly because forming them introduces ring strain. This ring strain is there even at the transition state, raising its energy and slowing down the reaction. $\Delta G^{\ddagger}$ is very large for a three-membered ring (due to strain) but decreases as the ring gets larger. This explains why three- and four-membered rings don't fit straightforwardly into the sequence.

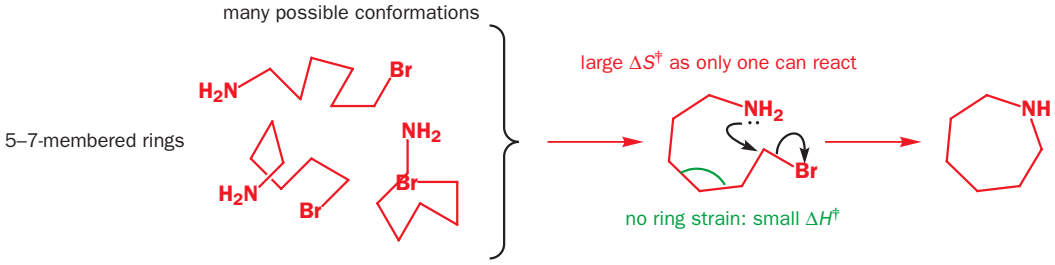


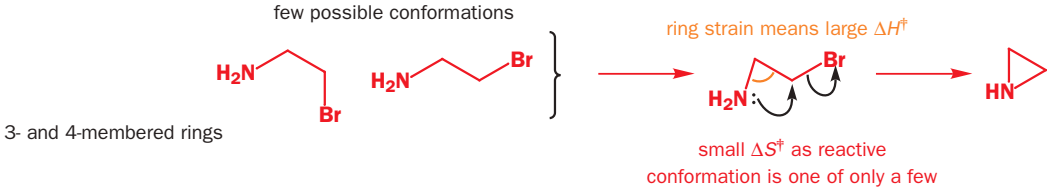
But, if the reaction rate simply depended on the strain of the product, the slowest reaction would be the formation of the three-membered ring, and six-membered rings (which are essentially strain-free) would form fastest. But as it is, four-membered rings form more slowly than three-membered ones, and five-membered ones faster than six-membered ones. To explain this, we need to remind you of an equation we presented in Chapter 13.

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$

The activation energy barriers $\Delta G^{\ddagger}$ of our reactions are made up of two parts: an enthalpy of activation $\Delta H^{\ddagger}$, which tells us about the energy required to bring atoms together against the strain and repulsive forces they usually have, and an entropy of activation $\Delta S^{\ddagger}$, which tells us about how easy it is to form an ordered transition state from a wriggling and randomly rotating molecule.

$\Delta G^{\ddagger}$ for three- and four-membered ring formation is large because $\Delta H^{\ddagger}$ is large: energy is needed to bend the molecule into the strained small-ring conformation. $\Delta H^{\ddagger}$ for five-, six-, and seven-membered rings is smaller: this is the quantifiable representation of the 'ring strain' factor we have just introduced. The second factor is one that depends on $\Delta S^{\ddagger}$: how much order must be imposed on the molecule to get it to react. Think of it this way: a long chain has a lot of disorder, and to get its ends to meet up and react means it has to give up a lot of freedom. So, for the formation of medium and large rings, $\Delta S^{\ddagger}$ is large and negative, contributing to a large $\Delta G^{\ddagger}$ and slow reactions. For three-membered rings, on the other hand, the reacting atoms are already very close together and almost no order needs to be imposed on the molecule to get it to cyclize: rotation about just one bond is all that is needed to ensure that the amine group is in the perfect position to attack the σ^* of the C–Br bond in our example above. $\Delta S^{\ddagger}$ is very small for three-membered rings so, while $\Delta H^{\ddagger}$ is large, there is little additional contribution from the $T\Delta S^{\ddagger}$ term and cyclization is relatively fast. Four-membered rings suffer the worst of both worlds: forming a four-membered ring introduces ring strain ($\Delta H^{\ddagger}$) *and* requires order ($\Delta S^{\ddagger}$) to be imposed on the molecule. They form very slowly as a result.





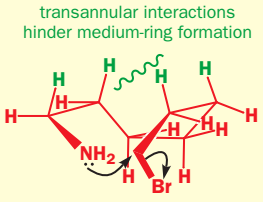
These results are summarized in the following box.

Ring formation

- Three-membered ring formation is fast—the product is strained so $\Delta H^{\ddagger}$ is large but this is offset by the reacting atoms being as close as they can get in a freely rotating chain
- Four-membered rings form slowly—the product is still significantly strained but the reacting atoms are now not right next to each other to offset this
- Five-membered ring formation is often fastest of all. Significantly less strain and the ends are still not too far apart
- Six-membered ring formation experiences no strain but neither does it have the advantage of the ends being close
- Seven-membered rings and beyond form more slowly as $\Delta S^{\ddagger}$ increases

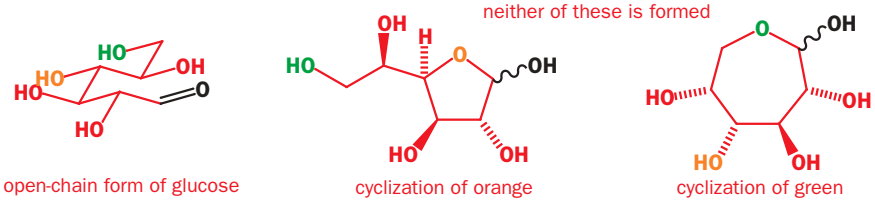
Medium and large rings

Beyond seven-membered rings, the rates stay low, but begin to level off, and may start to rise again when the rings have 10 or 11 members. These are the 'medium rings', of about 8–13 members, and they suffer from a different sort of strain, evident in the graph on p. 000 (Chapter 18), due to interactions between C–H bonds across the ring (**transannular interactions**). These are worst for rings of 8 and 9 members, and begin to be relieved once there are 10 or 11 atoms in the ring. For 14-membered rings and above, there is no transannular strain, and the rates of ring closure remain essentially constant at about the 7-membered ring mark. Rates of reactions in ring sizes of 14 and above are essentially little different from those in acyclic compounds. To get large rings to form, it is often necessary to carry out the cyclization reaction in very dilute solution to discourage competing intermolecular reactions.

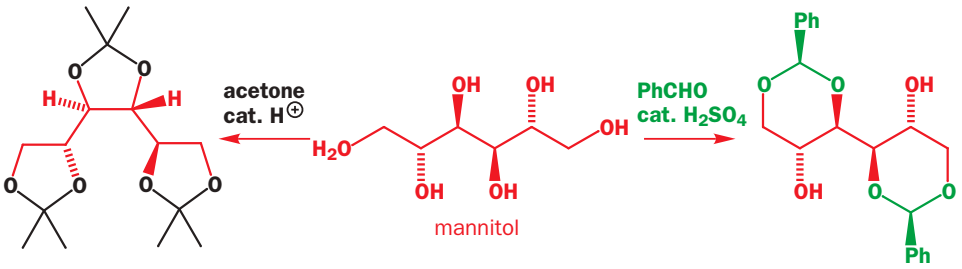


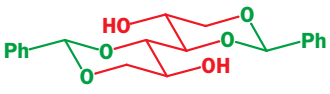
Thermodynamic control

In this section we have discussed the rate at which rings form: in other words the kinetics of ring formation. However, there are many ring-forming reactions that are under thermodynamic and not kinetic control. For example, you have already seen that glucose exists predominantly as a six-membered ring in solution. It could also exist as a five-membered ring: it doesn't because, although five-membered rings form faster than six-membered ones, they are usually less stable (remember, a six-membered ring is essentially strain-free). For similar thermodynamic reasons, it doesn't exist as a seven-membered ring, even though you can draw a reasonable structure for it.

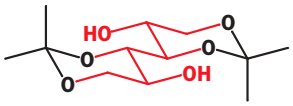


Thermodynamic control is important in other ways in carbohydrate chemistry, because control over ring size allows selective protection of the hydroxyl groups of sugars. Compare these two reactions. Both of them give acetals from the same starting material, mannitol.





all substituents equatorial



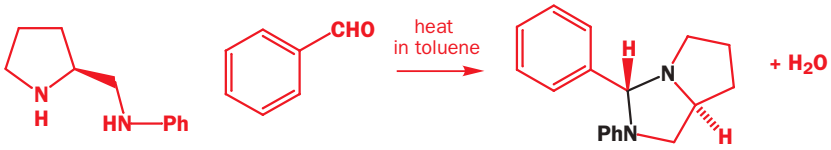
with acetone, axial methyl groups would be inevitable

Don't be put off by the way in which we have had to twist half the molecule round to draw the left-hand structure: the stereochemistry hasn't changed. The important thing is that acetone reacts with mannitol to form three five-membered acetals (dioxolanes) while benzaldehyde forms only two six-membered acetals. This is quite a common result: when there is a choice, acetone prefers to react across a 1,2-diol to give a five-membered ring, while aldehydes prefer to react across a 1,3-diol to form a six-membered ring. Drawing a conformational diagram of the product on the right helps to explain why. All of the substituents are equatorial, making this a particularly stable structure. Now imagine what would happen if acetone formed this type of six-membered ring acetal. There would always be an axial methyl group, and the six-membered rings would be less stable.

■ There is another example of selective protection using thermodyanmic control in Chapter 49, p. 000.

Aminals are another class of saturated heterocycles that form very readily under thermodynamic control: aminals are nitrogen analogues of acetals. They are usually made by refluxing a 1,2-diamine with an aldehyde in toluene (no acid catalyst is needed because the nitrogens are very nucleophilic), and this makes a very useful way of forming a chiral derivative of an achiral aldehyde. Here is an example: the diamine is made from the amino acid proline. The product has a new chiral centre, and it forms as a single diastereoisomer because the phenyl ring prefers to be on the *exo* face of the bicyclic system (see Chapter 33).

■ You should be able to write a mechanism for this reaction—it is much the same as the formation of an acetal, but no acid catalyst is present so you will not need to protonate the carbonyl groups before the amines attack.



1,2-diamine

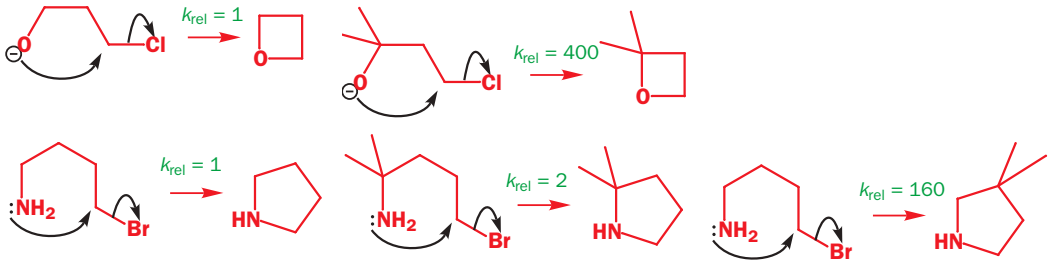
aminal functional group

Refluxing in toluene removes the water as an azeotrope (see p. 000), but, in fact, the aminal forms so readily that, if you do this reaction in cold dichloromethane (in which water is insoluble), the solution becomes cloudy as droplets of water are produced!

Combatting $\Delta S^{\ddagger}$—the Thorpe–Ingold effect

Compare the following relative rates for epoxide-forming cyclization reactions. The second looks as though it suffers more steric hindrance but it is tens of thousands of times faster!

Adding substituents to other ring-forming reactions makes them go faster too: in the next two examples the products are oxetanes and pyrrolidines.

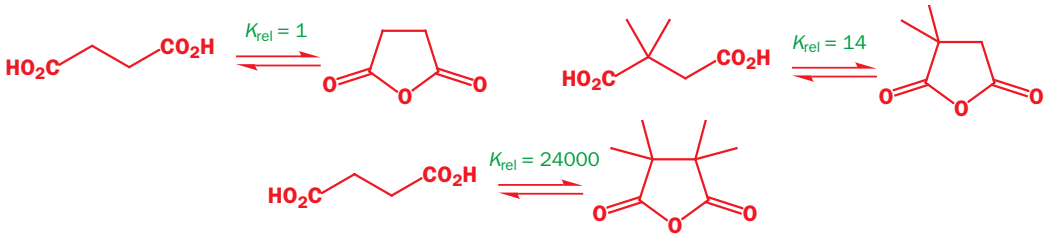


This effect is quite general, and is known as the **Thorpe–Ingold effect** after the first chemists to note its existence, in 1915.

The Thorpe–Ingold effect

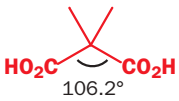
The Thorpe–Ingold effect is the way in which substituents on the ring increase the rate, or equilibrium constant, for ring-forming reactions.

As the box says, it's not only rate that can be affected by additional substitution. Here are the relative equilibrium constants for the formation of an anhydride from a 1,4-dicarboxylic acid (the unsubstituted acid is called succinic acid, and the values are scaled so that K_{rel} for the formation of succinic anhydride is 1). More substituents mean more cyclized product at equilibrium. The Thorpe–Ingold effect is both a kinetic and a thermodynamic phenomenon.

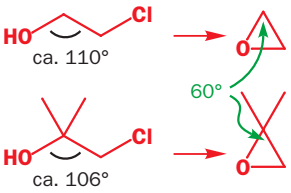


Now we need to explain why this is. The explanation comes in two parts, one of which may be more important than the other, depending on the ring being formed. The first part is more applicable to the formation of small rings, such as the first example we gave you.

If you measure the bond angles of chains of carbon atoms, you expect them to be close to the tetrahedral angle, 109.5°. The crystal structure of the 1,3-dicarboxylic acid in the margin, for example, shows a C–C–C bond angle of 110°. Now, imagine adding substituents to the chain. They will repel the carbon atoms already there, and force them a little closer than they were, making the bond angle slightly less. X-ray crystallography tells us that adding two methyl groups to our 1,3-dicarboxylic acid decreases the bond angle by about 4°.

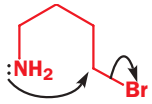


We can assume that the same is true in the alcohol starting materials for the epoxide-forming reactions (we can't measure the angle directly because the compounds aren't crystalline). Now consider what happens when both of these alcohols form an epoxide. The bond angle has to become about 60°, which involves about 50° of strain for the first diacid, but only 46° for the second. By distorting the starting material, the methyl groups have made it slightly easier to form a ring.



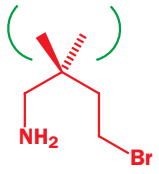
This part of the argument works only for small rings. For larger rings, we need another explanation, and it involves entropy. We'll use the pyrrolidine-forming reaction as an example. We have explained the effect of $\Delta S^{\ddagger}$ (entropy of activation) on the rate of ring formation: as larger rings form they have to lose more entropy at the transition state, and this contributes to a less favourable $\Delta G^{\ddagger}$.

lowest energy conformation – many others possible: high ΔS^{0}

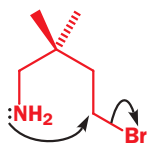


very negative $\Delta S^{\ddagger}$ to get to transition state

But, when the starting material has more substituents, it starts off with less entropy anyway. More substituents mean that some conformations are no longer accessible to the starting material—the green arcs below show how the methyl groups hinder rotation of the N and Br substituents into that region of space. Of those fewer conformations, many approximate to the conformation in the transition state, and moving from starting material to transition state involves a small loss of entropy: $\Delta S^{\ddagger}$ is less negative so $\Delta G^{\ddagger}$ ($= \Delta H^{\ddagger} - T\Delta S^{\ddagger}$) is more negative and the ring forms faster.



few conformations possible: lower ΔS^{0}

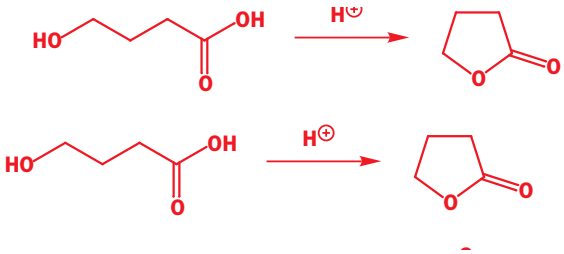


$\Delta S^{\ddagger}$ less negative

Because the same arguments apply to ΔS^{o} for the reaction as a whole (the difference in entropy between starting material and products), increased substitution favours ring closure even under thermodynamic control.

Baldwin's rules

Nearly all of the cyclization reactions that we have discussed have been intramolecular S_N2 reactions where one end of the molecule acted as the nucleophile displacing the leaving group on the other end. We kept to this sort of reaction in order to make valid comparisons between different ring sizes. But you can imagine making saturated heterocycles in plenty of other ways—intramolecular substitution at a carbonyl group, for example, such as happens in this lactonization reaction, or intramolecular addition on to an alkyne.

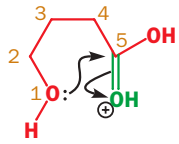


■ Oxyanions add readily to alkynes: see Chapter 31, p. 000.

Cyclization reactions can be classified by a simple system involving: (1) the ring size being formed; (2) whether the bond that breaks as the ring forms is inside (*endo*) or outside (*exo*) the new ring; and (3) whether the electrophile is an sp (digonal), sp^2 (trigonal), or sp^3 (tetrahedral) atom. This system places three of the cyclizations just shown in the following classes.

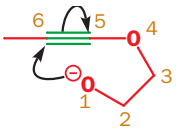
3-*exo*-*tet*

1. The ring being formed has three members; the breaking C–Br bond is outside the new ring (*exo*); the C carrying Br is a tetrahedral (sp^3) atom (*tet*)



5-*exo*-*trig*

2. The ring being formed has five members; the breaking C=O bond is outside the new ring (*exo*); the C being attacked is a trigonal (sp^2) atom (*trig*)



6-*endo*-*dig*

3. The ring being formed has six members; the breaking C≡C bond is inside the new ring (*endo*); the C being attacked is a digonal (sp) atom (*dig*)

■ Professor Sir Jack Baldwin is at Oxford and published his Rules in 1976 while at the Massachusetts Institute of Technology. He has studied biosynthesis (the way living things make molecules) extensively, especially in relation to the penicillins, and has applied many biosynthetic ideas to laboratory synthetic problems.

The classes of cyclization reactions are important, not because we have a compulsive Victorian desire to classify everything, but because which class a reaction falls into determines whether or not it is likely to work. Not all cyclizations are successful, even though they may look fine on paper! The guidelines that describe which reactions will work are known as **Baldwin's rules**: they are not really rules in the Woodward–Hoffmann sense of the term, but more empirical observations backed up by some sound stereoelectronic reasoning. To emphasize this, the rules are couched in terms of 'favoured' and 'disfavoured', rather than 'allowed' and 'forbidden'. We will deal with the rules step by step and then summarize them in a table at the end.

Firstly, and not surprisingly (because we have been talking about them for much of this chapter):

● **All *exo*-*tet* cyclizations are favoured.**

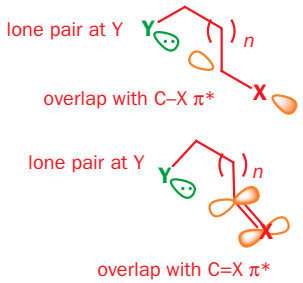
and, similarly (again you can find many examples in this book):

● **All *exo*-*trig* cyclizations are favoured.**

► This is a key difference. The Woodward–Hoffmann rules (Chapters 35 and 36) were deduced from theory, and examples were gradually discovered that fitted them. They cannot be violated: a reaction that disobeys the Woodward–Hoffmann rules is getting around them by following a different mechanism. Baldwin's rules were formulated by making observations of reactions that do, or do not, work.

Despite the variation in rate we have described for this type of reaction, *exo-tet* cyclizations have no stereoelectronic problems: the lone pair and the C–X σ* (X is the leaving group) can overlap successfully irrespective of ring size. The ring closures in Table 42.2 all fall into this category.

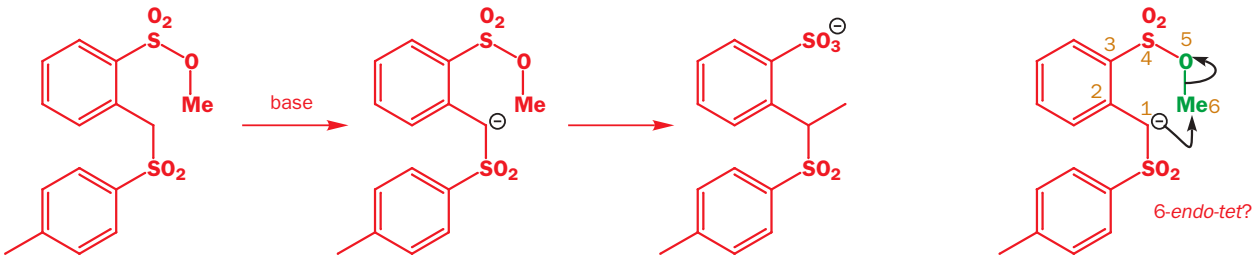
The same is true for *exo-trig* reactions: it is easy for the nucleophilic lone pair to overlap with the C=X π* to form a new bond. Examples include lactone formation such as the one on p. 000.



Endo-tet reactions are rather different. For a start:

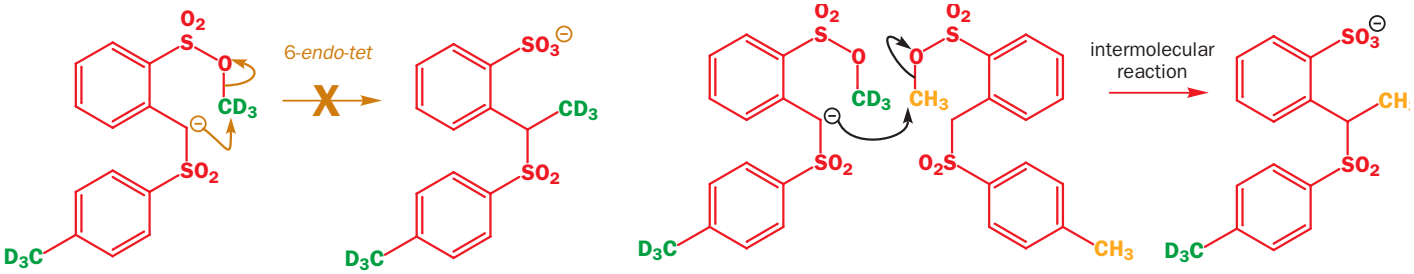
● 5- and 6-*endo-tet* are disfavoured.

Endo-tet reactions would not actually make a ring, but they fall conveniently into the system and we will look at them here. Here is a reaction that looks as though it contradicts what we have just said. The arrows in the reasonable-looking mechanism on the right describe a 6-*endo-tet* process, because the breaking Me–O bond is within the six-membered ring transition state (even if no ring is formed).



But Eschenmoser showed that, for all its appeal (intramolecular reactions usually outpace all alternatives), this mechanism is wrong. He mixed together the starting material for the reaction above with the hexadeuterated compound shown below, and re-ran the reaction. If the reaction had been intramolecular, the products would have contained either no deuterium, or six deuteriums. In the event, the product mixture contained about 25% of each of these compounds, with a further 50% containing three deuteriums. The products cannot have been formed intramolecularly, and this distribution is exactly what would be expected from an *inter*molecular reaction.

■ This is a **crossover experiment**. See Chapter 41, p. 000.

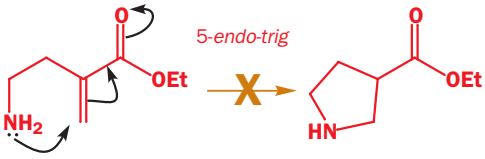


With *endo-trig* reactions, whether they work or not depends on the ring size.

● 3-, 4-, and 5-*endo-trig* are disfavoured; 6- and 7-*endo-trig* are favoured.

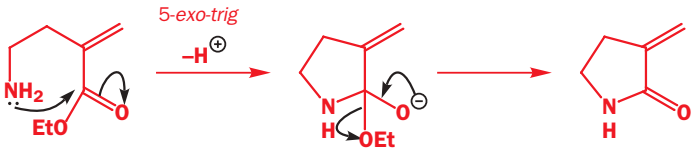
The most important reaction of the *endo-trig* class is the disfavoured 5-*endo-trig* reaction and, if there is one message you take away from this section, it should be that 5-*endo-trig* reactions are

disfavoured. The reason we say this is that 5-*endo-trig* cyclizations are reactions that look perfectly fine on paper, and at first sight it seems quite surprising that they won't work. This intramolecular conjugate addition, for example, appears to be a reasonable way of making a substituted pyrrolidine.



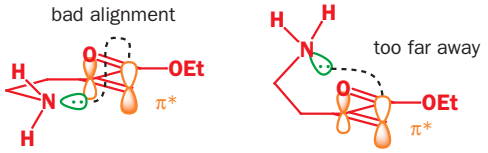
But this reaction doesn't happen: instead, the amine attacks the carbonyl group in a (favoured) 5-*exo-trig* cyclization.

▶ Amines usually undergo conjugate addition to unsaturated esters: see Chapter 10.

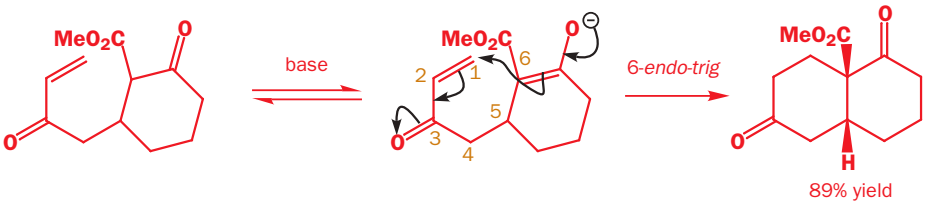


▶ It's easier to see this with a model, and if you have a set of molecular models you should make one to see for yourself.

Why is 5-*endo-trig* so bad? The problem is that the nitrogen's lone pair has problems reaching round to the π* orbital of the Michael acceptor. There is no problem reaching as far as the electrophilic carbon in the plane of the substituents but, if it bends out of this plane, which it must if it is to overlap with the π* orbitals, it moves too far away from the methylene carbon to react. It's like a dog chained just out of reach of a bone.

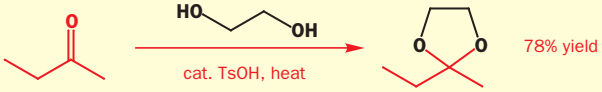


Lengthen the chain, though, and the dog gets his dinner. Here's a perfectly straightforward 6-*endo-trig*, for which orbital overlap presents no problem.

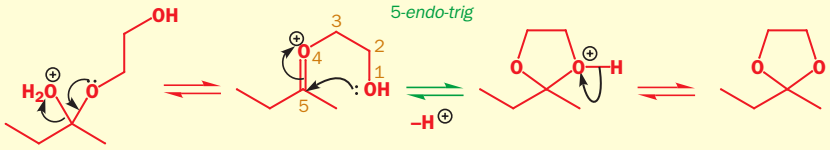


Exceptions to Baldwin's rules

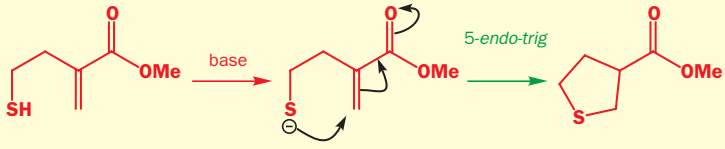
Baldwin's rules are only guidelines and, when a reaction is thermodynamically very favourable (Baldwin's rules, of course, describe the *kinetic* favourability of a reaction) and there is no other possible pathway, 5-*endo-trig* reactions *can* take place. The most striking example is one that you met quite early on in this book (Chapter 14): the formation of a cyclic acetal (dioxolane) from a carbonyl compound and ethylene glycol.



We don't need to give again the full mechanism here, but you should check that you can still write it. The key step with regard to Baldwin's rules is shown with a green arrow. It's a 5-*endo-trig* reaction but it works!



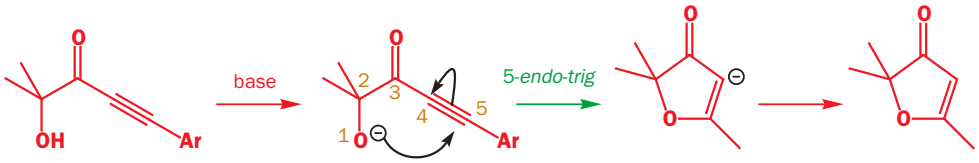
In fact, cations frequently disobey Baldwin's rules. Other well-defined exceptions to Baldwin's rules include pericyclic reactions and reactions in which second-row atoms such as sulfur are included in the ring. This 5-*endo-trig* reaction, the sulfur analogue of the amine cyclization that didn't work, is fine. C–S bonds are long, and the empty 3d orbitals of sulfur may play a role by providing an initial interaction with the C–C π orbital.



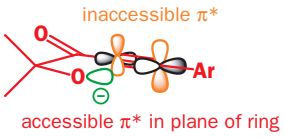
With *tet* and *trig* cyclizations, *exo* is better than *endo*; with *dig* cyclizations, the reverse is true.

● **All *endo-dig* cyclizations are favoured.**

Move from 5-*endo-trig* to 5-*endo-dig*, and the reactions become much easier: even 4-*endo-dig* reactions work. Here is an example of 5-*endo-dig*.



We warned you to look out for 5-*endo-trig* reactions because they are disfavoured even though on paper they look fine. Now the alert is the other way round! We expect you'd agree that these *endo-dig* reactions look awful on paper: the linear alkyne seems to put the electrophilic carbon well out of reach of the nucleophile, even further away than in the 5-*endo-trig* reaction. The important thing with *endo-dig* cyclizations, though, is that the alkyne has two π* orbitals, one of which must always lie in the plane of the new ring, making it much easier for the nucleophile to get at.



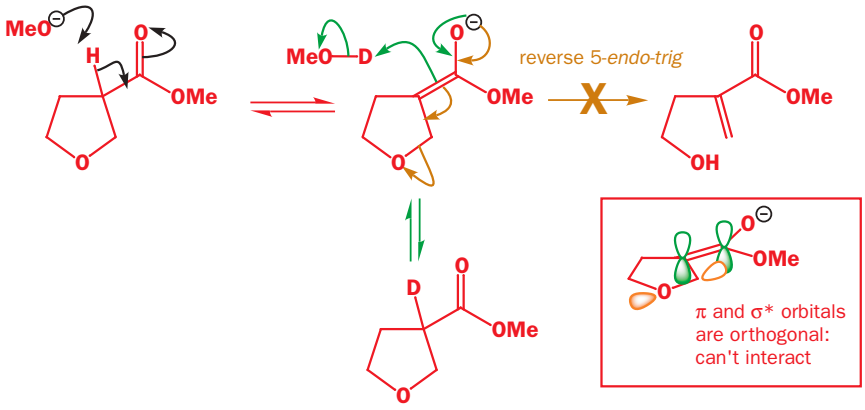
Conversely:

● **3- and 4-*exo-dig* are disfavoured; 5- to 7-*exo-dig* are favoured.**

These reactions are less important and we will not discuss them in detail.

Baldwin's rules and ring opening

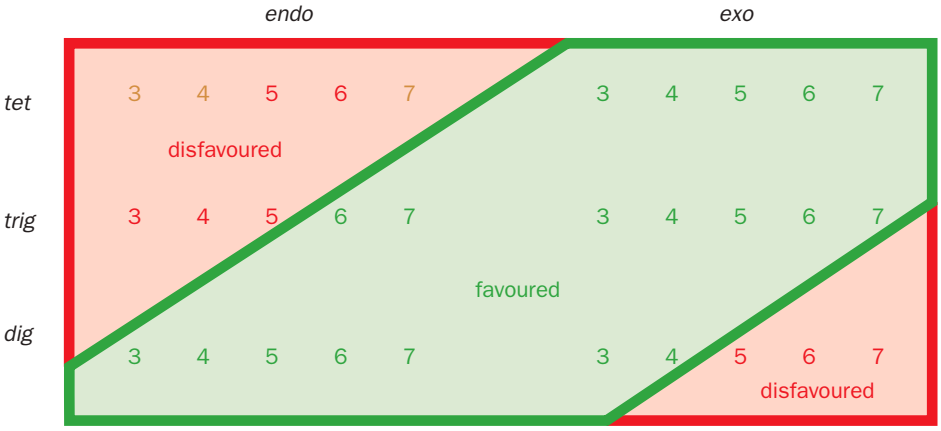
Baldwin's rules work because they are based on whether or not orbital overlap can be readily achieved in the conformation required at the transition state. You met in the last chapter the **principle of microscopic reversibility**, which says that, if a reaction goes via a certain mechanism, the reverse reaction must follow exactly the same path in the opposite direction. So Baldwin's rules also work for ring-opening reactions. This is where the unfavourability of 5-*endo-trig* really is important: this tetrahydrofuranyl ester, for example, looks set up to do an E1cB elimination in base. Indeed , when it is treated with methoxide in deuterated methanol it exchanges the proton α to the ester for deuterium, proving that the enolate forms. But is does not eliminate: elimination would be a reverse 5-*endo-trig* process and is disfavoured.



Whenever you think about a ring-opening reaction, consider its reverse, and think whether it is favoured according to Baldwin's rules.

To summarize

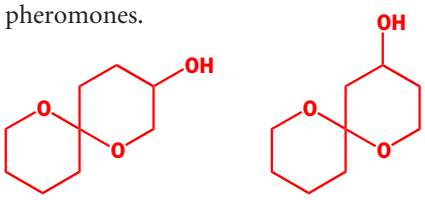
We shall end by summarizing Baldwin's rules in a chart. You should note the general outline of this chart: commit to memory that, broadly speaking, *endo-tet* and *endo-trig* are disfavoured; *exo-tet* and *exo-trig* are favoured, and the reverse for *dig*. Then you just need to learn the cut-off points that indicate the exceptions to this broad-brush view: 6-*endo-trig* falls into the favoured catergory while 5-*exo-dig* falls into the disfavoured one. And, if you really can remember only one thing, it should be that 5-*endo-trig* is disfavoured!



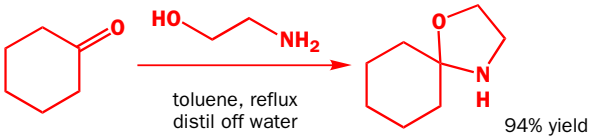
In the next two chapters, we continue with heterocycles, but move from saturated ones to flat, aromatic ones. Conformation and stereoelectronics are no longer issues, but molecular orbitals certainly are. In Chapter 44 you will meet many cyclization reactions: you will find that not a single one is Baldwin-disfavoured.

Problems

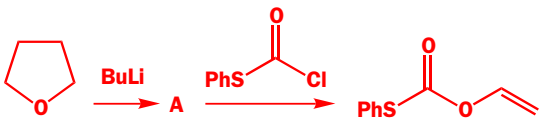
1. Predict the most favourable conformations of these insect pheromones.



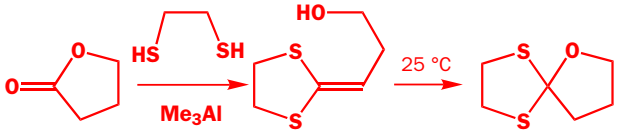
2. Refluxing cyclohexanone with ethanolamine in toluene with a Dean Stark separator to remove the water gives an excellent yield of this spirocycle. What is the mechanism, and why is acid catalysis (or any other kind) unnecessary?



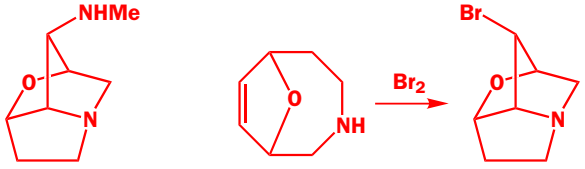
3. What is A in the following reaction scheme and how does it react to give the final product?



4. Give mechanisms for the formation of this *spiro* heterocycle. Why is the product not formed simply on reacting the starting materials in acid solution without Me_3Al?

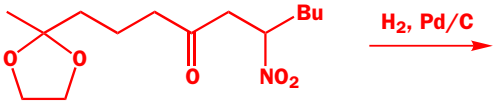


5. The *Lolium* alkaloids have a striking skeleton of saturated heterocycles. One way to make this skeleton is shown below. Explain both the mechanism and the stereochemistry.

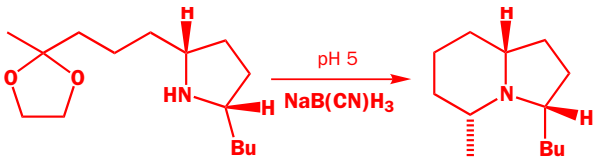


a *Lolium* alkaloid

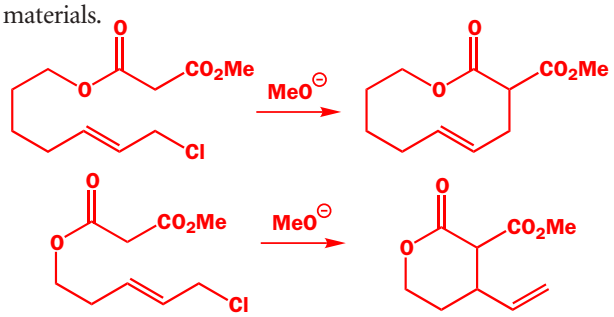
6. Explain the stereochemical control in this synthesis of a fused bicyclic saturated heterocycle—the trail pheromone of an ant.



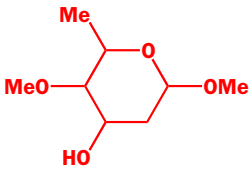
Continued opposite



7. In Chapter 31, one of the problems asked you to comment on the difference between these two reactions. Now would you like to comment again and add comments on the way we drew the starting materials.



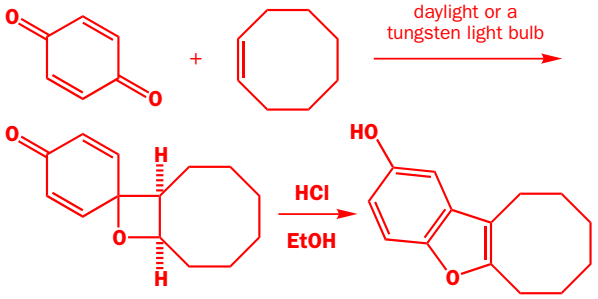
8. In Chapter 32, Problem 6, we asked you to work out the stereochemistry of a sugar. One of the sugar components in the antibiotic kijanimycin has the gross structure and NMR spectrum shown below. What is its stereochemistry? Signals marked * exchange with D_2O.



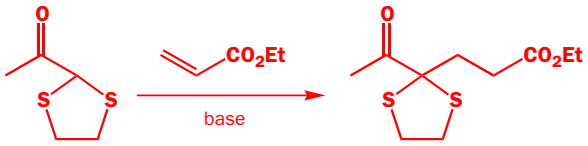
δ_H 1.33 p.p.m. (3H, d, *J* 6 Hz), 1.61* p.p.m. (1H, broad s), 1.87 p.p.m. (1H, ddd, *J* 14, 3, 3.5 Hz), 2.21 p.p.m. (1H, ddd, *J* 14, 3, 1.5 Hz), 2.87 p.p.m. (1H, dd, *J* 10, 3 Hz), 3.40 p.p.m. (3H, s), 3.47 p.p.m. (3H, s), 3.99 p.p.m. (1H, dq, *J* 10, 6 Hz), 1.33 p.p.m. (3H, d, *J* 6 Hz), 4.24 p.p.m. (1H, ddd, *J* 3, 3, 3.5 Hz), and 4.79 p.p.m. (1H, dd, *J* 3.5, 1.5 Hz).

When you did this problem, you probably thought about the conformation but now draw it and say why you think the molecule prefers that conformation.

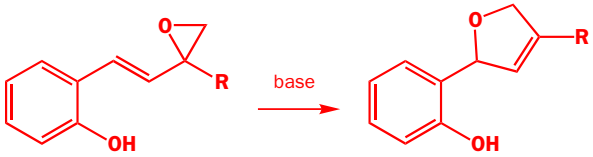
9. Revision of Chapters 35 and 37. Give mechanisms for these reactions, commenting on the formation of that particular saturated heterocycle in the first reaction. What is the alternative product from the migration and why is it not formed?



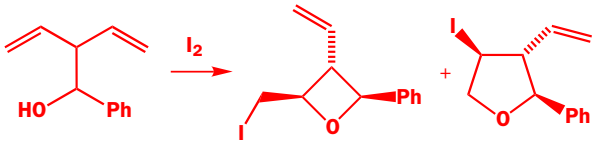
10. Though the anion of dithiolane decomposes as described in the chapter and cannot be used as a d^1 reagent, the example shown here works well without any decomposition. Explain and comment on the regioselectivity of the reaction. Anions of dithianes are notorious for preferring direct to conjugate addition.



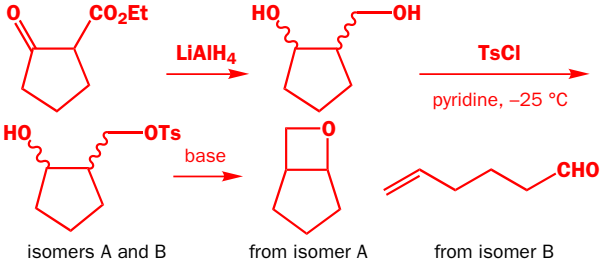
11. Propose a mechanism for this reaction. It does not occur in the absence of an *ortho*- or a *para*-OH group.



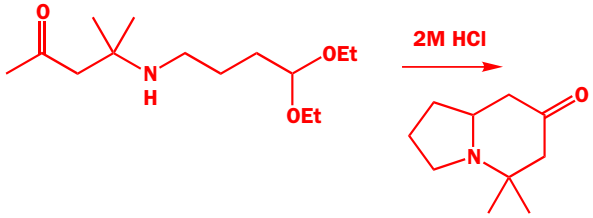
12. Explain why this cyclization gives a preponderance (3:1) of the oxetane though the tetrahydrofuran is much more stable.



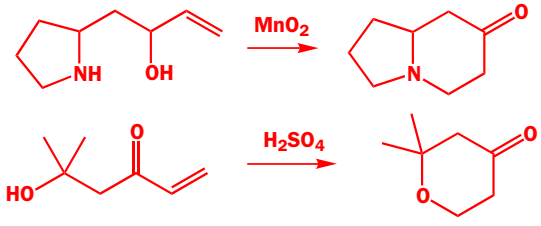
13. Reduction of this keto-ester with $LiAlH_4$ gives a mixture of diastereoisomers of the diol. Treatment with TsCl and pyridine at –25 °C gives a monotosylate from each. Treatment of these with base leads to the two very different products shown. Explain.



14. Draw a mechanism for the following multistep reaction. Do the cyclization steps follow Baldwin's rules? What other stereoelectronic effects are involved?



15. Consider the question of Baldwin's rules for each of these reactions. Why do you think they are successful?



Aromatic heterocycles 1: structures and reactions

43

Connections

Building on:

- Aromaticity ch7
- Electrophilic aromatic substitution ch22
- Nucleophilic attack on aromatic rings ch23
- Saturated heterocycles ch42

Arriving at:

- Aromatic systems conceptually derived from benzene: replacing CH with N to get pyridine
- Replacing CH=CH with N to get pyrrole
- How pyridine reacts
- How pyridine derivatives can be used to extend pyridine's reactivity
- How pyrrole reacts
- How furan and thiophene compare with pyrrole
- Putting more nitrogens in five- and six-membered rings
- Fused rings: indole, quinoline, isoquinoline, and indolizine
- Rings with nitrogen and another heteroatom: oxygen or sulfur
- More complex heterocycles: porphyrins and phthalocyanines

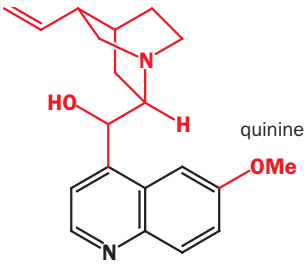
Looking forward to:

- Synthesis of aromatic heterocycles ch44
- Biological chemistry ch49–ch51

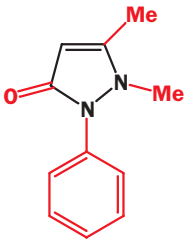
Introduction

Benzene is aromatic because it has six electrons in a cyclic conjugated system. We know it is aromatic because it is exceptionally stable and it has a ring current and hence large chemical shifts in the proton NMR spectrum as well as a special chemistry involving substitution rather than addition with electrophiles. This chapter and the next are about the very large number of other aromatic systems in which one or more atoms in the benzene ring are replaced by heteroatoms such as N, O, and S. There are thousands of these systems with five- and six-membered rings, and we will examine just a few.

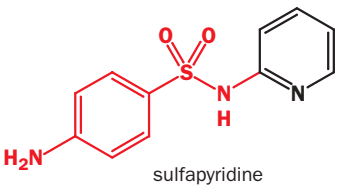
Our subject is **aromatic heterocycles** and it is important that we treat it seriously because most—probably about two-thirds of—organic compounds belong to this class, and they number among them some of the most significant compounds for human beings. If we think only of drugs we can define the history of medicine by heterocycles. Even in the sixteenth century quinine was used to prevent and treat malaria, though the structure of the drug was not known. The first synthetic drug was antipyrine (1887) for the reduction of fevers. The first effective antibiotic was sulfapyridine (1938). The first multi-million pound drug (1970s) was Tagamet, the anti-ulcer drug, and among the most topical of current drugs is Viagra (1997) for treatment of male impotence.



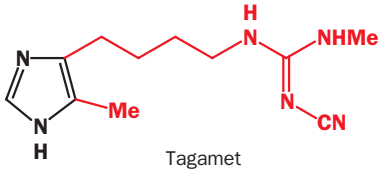
quinine



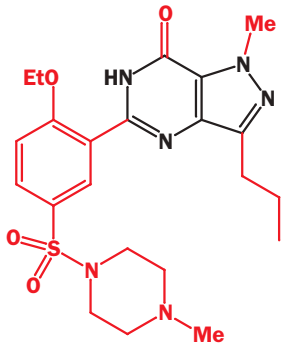
antipyrine



sulfapyridine



Tagamet



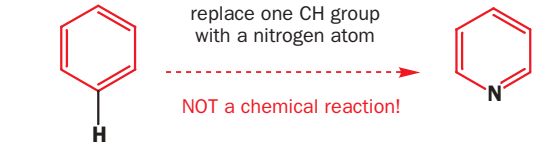
Viagra

■ Sir James Black, discoverer of Tagamet, worked on medicinal chemistry at Smith Kline French (later SmithKline Beecham) and was awarded the Nobel Prize for his analysis of drug receptors in 1988.

All these compounds have heterocyclic aromatic rings shown in black. Three have single rings, five- or six-membered, two have five- or six-membered rings fused together. The number of nitrogens in the rings varies from one to four. We will start by looking at the simple six-membered ring with one nitrogen atom. This is pyridine and the drug sulfapyridine is an example.

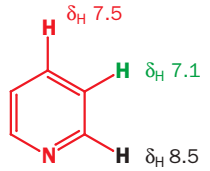
Aromaticity survives when parts of benzene's ring are replaced by nitrogen atoms

There is no doubt that benzene is aromatic. Now we must ask: how can we insert a heteroatom into the ring and retain aromaticity? What kind of atom is needed? If we want to replace one of the carbon atoms of benzene with a heteroatom, we need an atom that can be trigonal to keep the flat hexagonal ring and that has a p orbital to keep the six delocalized electrons. Nitrogen is ideal so we can imagine replacing a CH group in benzene with a nitrogen atom.



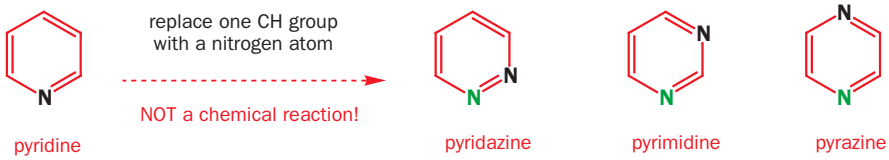
The orbitals in the ring have not changed in position or shape and we still have the six electrons from the three double bonds. One obvious difference is that nitrogen is trivalent and thus there is no NH bond. Instead, a lone pair of electrons occupies the space of the C–H bond in benzene.

In theory then, pyridine is aromatic. But is it in real life? The most important evidence comes from the proton NMR spectrum. The six protons of benzene resonate at δ_H 7.27 p.p.m., some 2 p.p.m. downfield from the alkene region, clear evidence for a ring current (Chapter 11). Pyridine is not as symmetrical as benzene but the three types of proton all resonate in the same region.



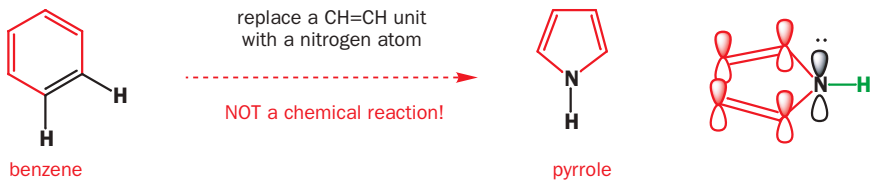
^{1}H NMR spectrum of pyridine

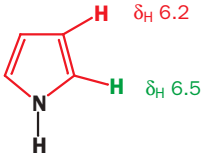
As we will see, pyridine is also very stable and, by any reasonable assessment, pyridine is aromatic. We could continue the process of replacing, on paper, more CH groups with nitrogen atoms, and would find three new aromatic heterocycles—pyridazine, pyrimidine, and pyrazine:



▶ One of the most annoying things about heterocyclic chemistry is the mass of what appear to be illogical names. You should not, of course, attempt to learn them all, but a basic idea of how they are designed will help you. We will give you a guide on which names to learn shortly. For the moment accept that 'amine' ends in '-ine' and any heterocyclic compound whose name ends in '-ine' is a nitrogen heterocycle. The syllable 'azo-' also implies nitrogen and 'pyr-' (usually) implies a six-membered ring. (except in pyrrole!)

There is another way in which we might transform benzene into a heterocycle. Nitrogen has a lone pair of electrons so we could replace a CH=CH unit in benzene by a nitrogen atom providing that we can use the lone pair in the delocalized system. This means putting it into a p orbital.





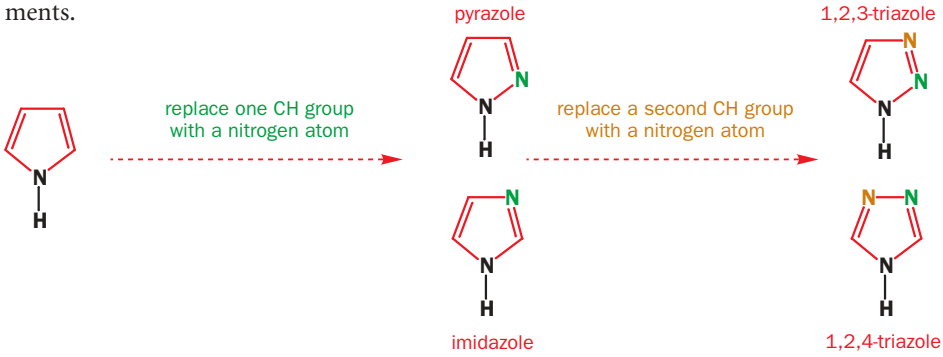
δ_H~10

We still have the four electrons from the remaining double bonds and, with the two electrons of the lone pair on nitrogen, that makes six in all. The nitrogen atom must still be trigonal with the lone pair in a p orbital so the N–H bond is in the plane of the five-membered ring.

The NMR of pyrrole is slightly less convincing as the two types of proton on the ring resonate at higher field (6.5 and 6.2 p.p.m.) than those of benzene or pyridine but they still fall in the aromatic rather than the alkene region. Pyrrole is also more reactive towards electrophiles than benzene or

pyridine, but it does the usual aromatic substitution reactions (Friedel–Crafts, nitration, halogenation) rather than addition reactions: pyrrole is also aromatic.

Inventing heterocycles by further replacement of CH groups by nitrogen in pyrrole leads to two compounds, pyrazole and imidazole, after one replacement and to two triazoles after two replacements.

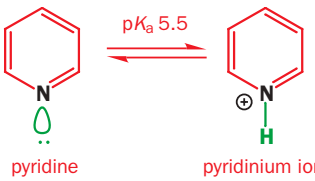


All of these compounds are generally accepted as aromatic too as they broadly have the NMR spectra and reactivities expected for aromatic compounds. As you may expect, introducing heteroatoms into the aromatic ring and, even more, changing the ring size actually affect the chemistry a great deal. We must now return to pyridine and work our way more slowly through the chemistry of these important heterocycles to establish the principles that govern their behaviour.

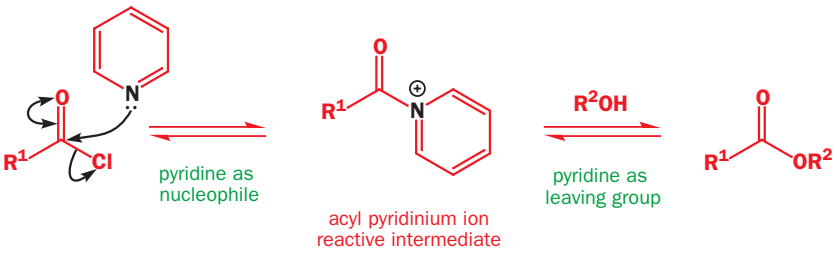
▶ The ending '-ole' is systematic and refers to a five-membered heterocyclic ring. All the five-membered aromatic heterocycles with nitrogen in the ring are sometimes called 'the azoles'. Strictly speaking, pyrrole is 'azole', pyrazole is '1,2-diazole', and imidazole is '1,3-diazole'. These names are not used but oxazole and thiazole are used for the oxygen and sulfur analogues of imidazole.

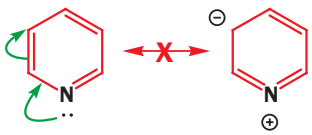
Pyridine is a very unreactive aromatic imine

The nitrogen atom in the pyridine ring is planar and trigonal with the lone pair in the plane of the ring. This makes it an imine. Most of the imines you have met before (in Chapter 14, for example), have been unstable intermediates in carbonyl group reactions, but in pyridine we have a stable imine—stable because of its aromaticity. All imines are more weakly basic than saturated amines and pyridine is a weak base with a pK_a of 5.5. This means that the pyridinium ion as about as strong an acid as a carboxylic acid.



Pyridine is a reasonable nucleophile for carbonyl groups and is often used as a nucleophilic catalyst in acylation reactions. Esters are often made in pyridine solution from alcohols and acid chlorides (the full mechanism is on p. 000 of Chapter 12).

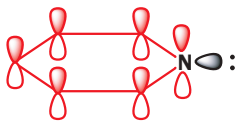




Pyridine is nucleophilic at the nitrogen atom because *the lone pair of electrons on nitrogen cannot be delocalized around the ring*. They are in an sp^2 orbital orthogonal to the p orbitals in the ring and there is no interaction between orthogonal orbitals. Try it for yourself, drawing arrows. All attempts to delocalize the electrons lead to impossible results!

● **The lone pair of pyridine's nitrogen atom is not delocalized.**

▶ Pyridine is also toxic and has a foul smell—so there are disadvantages in using pyridine as a solvent. But it is cheap and remains a popular solvent in spite of the problems.

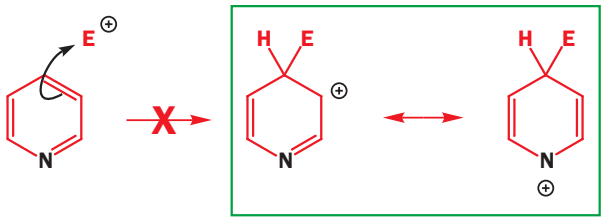


lone pair in sp^2 orbital at right angles to p orbitals in ring: no interaction between orthogonal orbitals

Our main interest must be this: what does the nitrogen atom do to the rest of the ring? The important orbitals—the p orbitals of the aromatic system—are superficially the same as in benzene, but the more electronegative nitrogen atom will lower the energy of all the orbitals. Lower-energy filled orbitals mean a *less* reactive nucleophile but a lower-energy LUMO means a *more* reactive electrophile. This is a good guide to the chemistry of pyridine. It is less reactive than benzene in electrophilic aromatic substitution reactions but nucleophilic substitution, which is difficult for benzene, comes easily to pyridine.

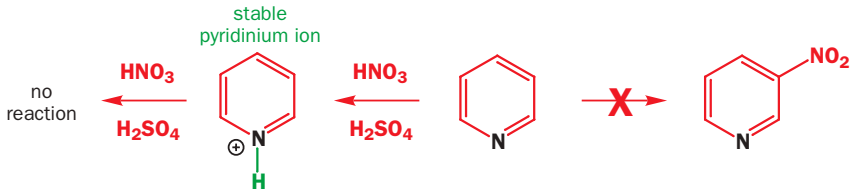
Pyridine is bad at electrophilic aromatic substitution

The lower energy of the orbitals of pyridine's π system means that electrophilic attack on the ring is difficult. Another way to look at this is to see that the nitrogen atom destabilizes the cationic would-be intermediate, especially at the 2- and 4-positions.

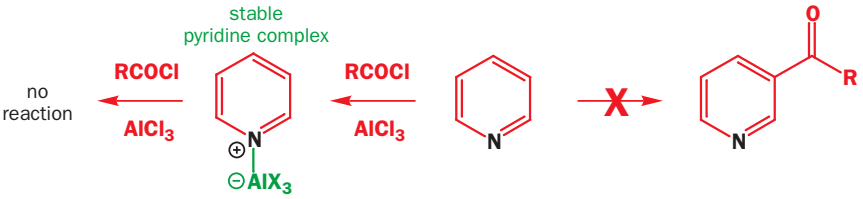


▶ Contrast the unstable electron-deficient cationic intermediate with the stable pyridinium ion. The nitrogen lone pair is used to make the pyridinium ion but is not involved in the unstable intermediate. Note that reaction at the 3-position is the *best* option but still doesn't occur. Reaction at the 2- and 4-positions is worse.

An equally serious problem is that the nitrogen lone pair is basic and a reasonably good nucleophile—this is the basis for its role as a nucleophilic catalyst in acylations. The normal reagents for electrophilic substitution reactions, such as nitration, are acidic. Treatment of pyridine with the usual mixture of HNO_3 and H_2SO_4 merely protonates the nitrogen atom. Pyridine itself is not very reactive towards electrophiles: the pyridinium ion is totally unreactive.



Other reactions, such as Friedel–Crafts acylations, require Lewis acids and these too react at nitrogen. Pyridine is a good ligand for metals such as Al(III) or Sn(IV) and, once again, the complex with its cationic nitrogen is completely unreactive towards electrophiles.

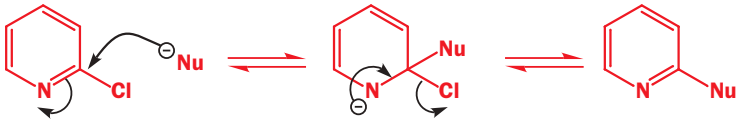


● Pyridine does not undergo electrolytic substitution

Aromatic electrophilic substitution on pyridine is not a useful reaction. The ring is unreactive and the electrophilic reagents attack nitrogen making the ring even less reactive. Avoid nitration, sulfonation, halogenation, and Friedel–Crafts reactions on simple pyridines.

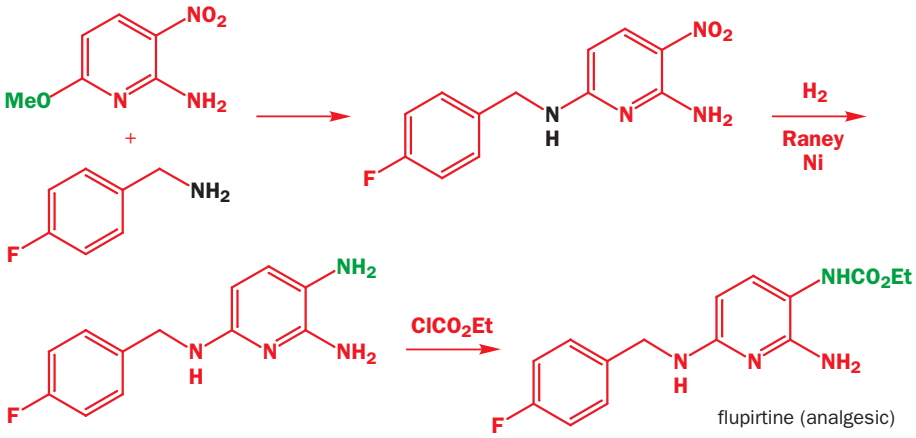
Nucleophilic substitution is easy with pyridines

By contrast, the nitrogen atom makes pyridines *more* reactive towards nucleophilic substitution, particularly at the 2- and 4-positions, by lowering the LUMO energy of the π system of pyridine. You can see this effect in action in the ease of replacement of halogens in these positions by nucleophiles.



The intermediate anion is stabilized by electronegative nitrogen and by delocalization round the ring. These reactions have some similarity to nucleophilic aromatic substitution (Chapter 23) but are more similar to carbonyl reactions. The intermediate anion is a tetrahedral intermediate that loses the best leaving group to regenerate the stable aromatic system. Nucleophiles such as amines or thiolate anions work well in these reactions.

The leaving group does not have to be as good as chloride in these reactions. Continuing the analogy with carbonyl reactions, 2- and 4-chloropyridines are rather like acid chlorides but we need only use less reactive pyridyl ethers, which react like esters, to make amides. The 2- and 4-methoxypyridines allow the completion of the synthesis of flupirtine.



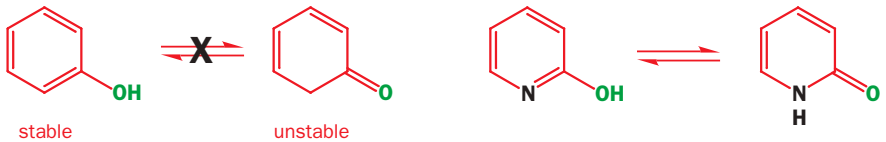
■ Two of the problems at the end of the chapter concern this synthesis: you might like to turn to them now.

The first step is a nucleophilic aromatic substitution. In the second step the nitro group is reduced to an amino group without any effect on the pyridine ring—another piece of evidence for its aromaticity. Finally, one amino group is acylated in the presence of three others.

Pyridones are good substrates for nucleophilic substitution

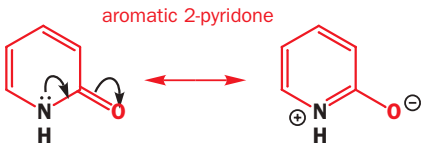
The starting materials for these nucleophilic substitutions (2- and 4- chloro or methoxypyridines) are themselves made by nucleophilic substitution on pyrid*ones* and we need now to discuss these interesting molecules. If you were asked to propose how 2-methoxypyridine might be made, you would probably suggest, by analogy with the corresponding benzene compound, alkylation of a phenol. Let us look at this in detail.

The starting material for this reaction is a 2-hydroxypyridine that can tautomerize to an amide-like structure by the shift of the acidic proton from oxygen to nitrogen. In the phenol series there is no doubt about which structure will be stable as the ketone is not aromatic; for the pyridine both structures are aromatic.

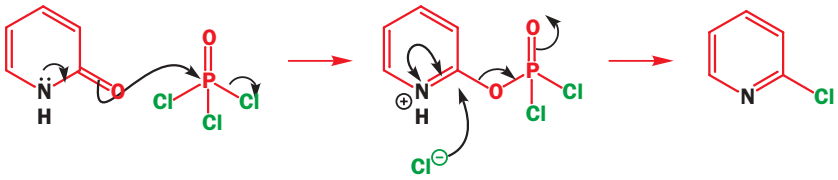


stable phenol — unstable non-aromatic

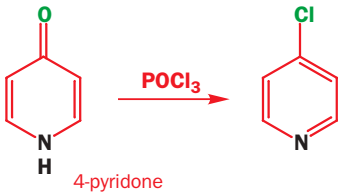
In fact, 2-hydroxypyridine prefers to exist as the 'amide' because that has the advantage of a strong C=O bond and is still aromatic. There are two electrons in each of the C=C double bonds and two also in the lone pair of electrons on the trigonal nitrogen atom of the amide. Delocalization of the lone pair in typical amide style makes the point clearer.



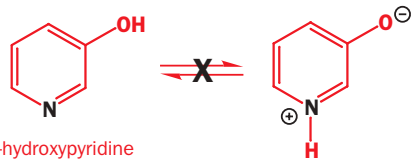
Pyridones are easy to prepare (see Chapter 44) and can be alkylated on oxygen as predicted by their structure. A more important reaction is the direct conversion to chloropyridines with $POCl_3$. The reaction starts by attack of the oxygen atom at phosphorus to create a leaving group, followed by aromatic nucleophilic substitution. The overall effect is very similar to acyl chloride formation from a carboxylic acid.



The same reaction occurs with 4-pyridone, which is also delocalized in the same way and exists in the 'amide' form; but not with 3-hydroxypyridine, which exists in the 'phenol' form.



4-pyridone



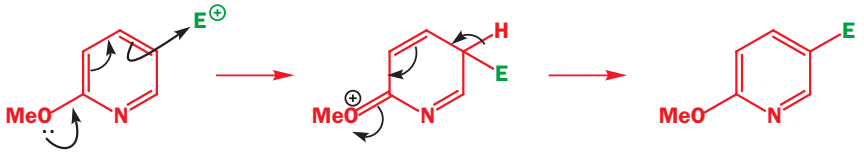
3-hydroxypyridine

Pyridines undergo nucleophilic substitution

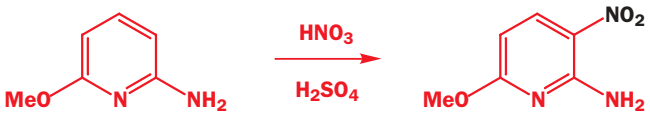
Pyridines can undergo *electrophilic* substitution only if they are activated by electron-donating substituents (see next section) but they readily undergo *nucleophilic* substitution without any activation other than the ring nitrogen atom.

Activated pyridines will do electrophilic aromatic substitution

Useful electrophilic substitutions occur only on pyridines having electron-donating substituents such as NH_2 or OMe. These activate benzene rings too (Chapter 22) but here their help is vital. They supply a nonbonding pair of electrons that becomes the HOMO and carries out the reaction. Simple amino- or methoxypyridines react reasonably well *ortho* and *para* to the activating group. These reactions happen in spite of the molecule being a pyridine, not because of it.

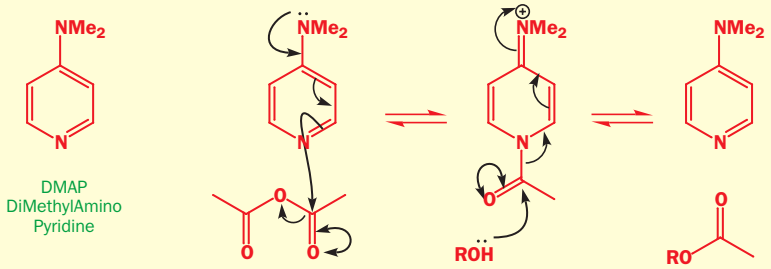


A practical example occurs in the manufacture of the analgesic flupirtine where a doubly activated pyridine having both MeO and NH_2 groups is nitrated just as if it were a benzene ring. The nitro group goes in *ortho* to the amino group and *para* to the methoxy group. This sequence is completed in the next section. The activation is evidently enough to compensate for the molecule being almost entirely protonated under the conditions of the reaction.



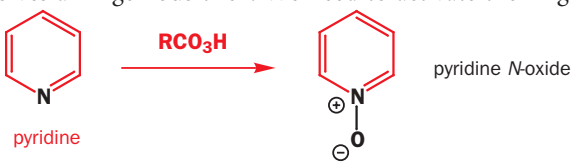
DMAP

One particular amino-pyridine has a special role as a more effective acylation catalyst than pyridine itself. This is DMAP (DiMethylAminoPyridine) in which the amino group is placed to reinforce the nucleophilic nature of the nitrogen atom. Whereas acylations 'catalysed' by pyridine are normally carried out in solution in pyridine, only small amounts of DMAP in other solvents are needed to do the same job.

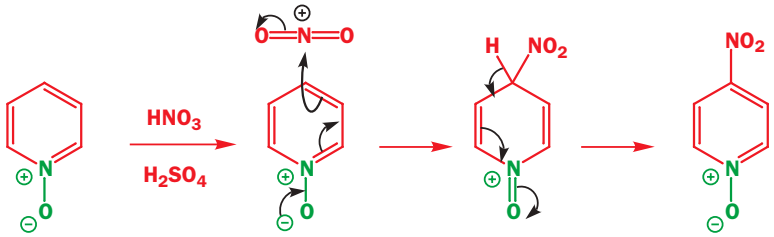


Pyridine *N*-oxides are reactive towards both electrophilic and nucleophilic substitution

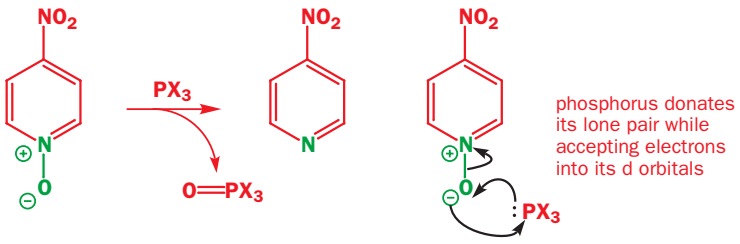
This is all very well if the molecule has such activating groups, but supposing it doesn't? How are we to nitrate pyridine itself? The answer involves an ingenious trick. We need to activate the ring with an electron-rich substituent that can later be removed and we also need to stop the nitrogen atom reacting with the electrophile. All of this can be done with a single atom!



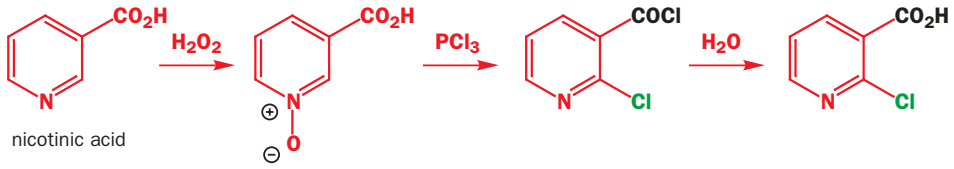
Because the nitrogen atom is nucleophilic, pyridine can be oxidized to pyridine *N*-oxide with reagents such as *m*-CPBA or just H_2O_2 in acetic acid. These *N*-oxides are stable dipolar species with the electrons on oxygen delocalized round the pyridine ring, raising the HOMO of the molecule. Reaction with electrophiles occurs at the 2- ('*ortho*') and 4- ('*para*') positions, chiefly at the 4-position to keep away from positively charged nitrogen.



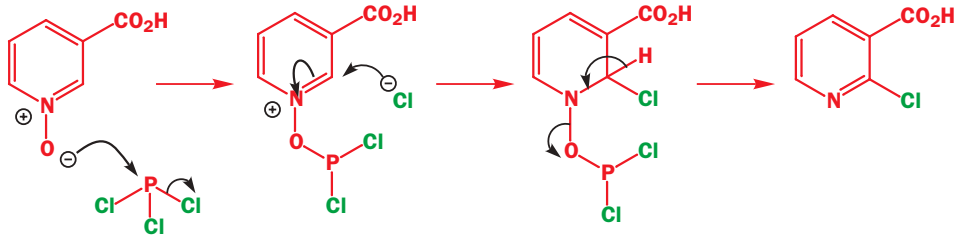
Now the oxide must be removed and this is best done with trivalent phosphorus compounds such as $(MeO)_3P$ or PCl_3. The phosphorus atom detaches the oxygen atom in a single step to form the very stable P=O double bond. In this reaction the phosphorus atom is acting as both a nucleophile and an electrophile, but mainly as an electrophile since PCl_3 is more reactive here than $(MeO)_3P$.



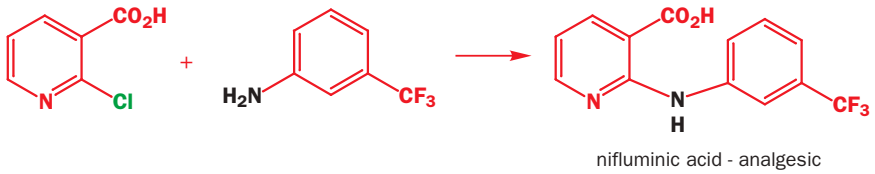
The same activation that allowed simple electrophilic substitution—oxidation to the *N*-oxide—can also allow a useful nucleophilic substitution. The positive nitrogen atom encourages nucleophilic attack and the oxygen atom can be turned into a leaving group with PCl_3. Our example is nicotinic acid whose biological importance we will discuss in Chapter 50.



The *N*-oxide reacts with PCl_3 through oxygen and the chloride ion released in this reaction adds to the most electrophilic position between the two electron-withdrawing groups. Now a simple elimination restores aromaticity and gives a product looking as though it results from chlorination rather than nucleophilic attack.



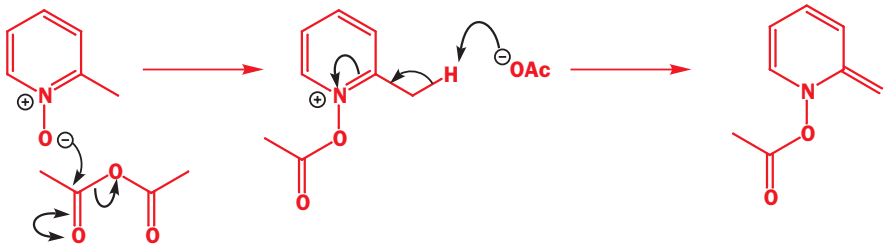
The reagent PCl_3 also converts the carboxylic acid to the acyl chloride, which is hydrolysed back again in the last step. This is a useful sequence because the chlorine atom has been introduced into the 2-position from which it may in turn be displaced by, for example, amines.



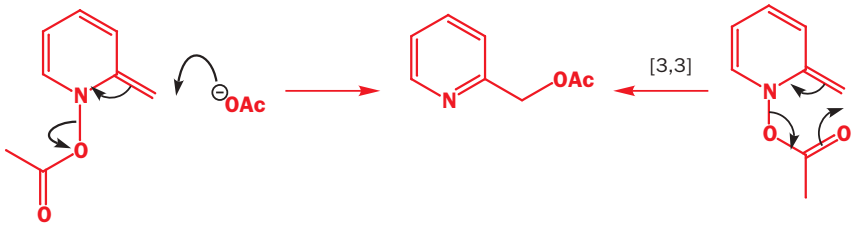
● Pyridine-*N*-oxides

Pyridine *N*-oxides are useful for both electrophilic and nucleophilic substitutions on the same carbon atoms (2-, 4-, and 6-) in the ring.

Nucleophilic addition at an even more distant site is possible on reaction with acid anhydrides if there is an alkyl group in the 2-position. Acylation occurs on oxygen as in the last reaction but then a proton is lost from the side chain to give an uncharged intermediate.



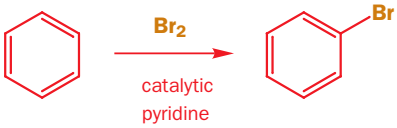
This compound rearranges with migration of the acetate group to the side chain and the restoration of aromaticity. This may be an ionic reaction or a [3,3]-sigmatropic rearrangement.



Since pyridine is abundant and cheap and has an extremely rich chemistry, it is not surprising that it has many applications.

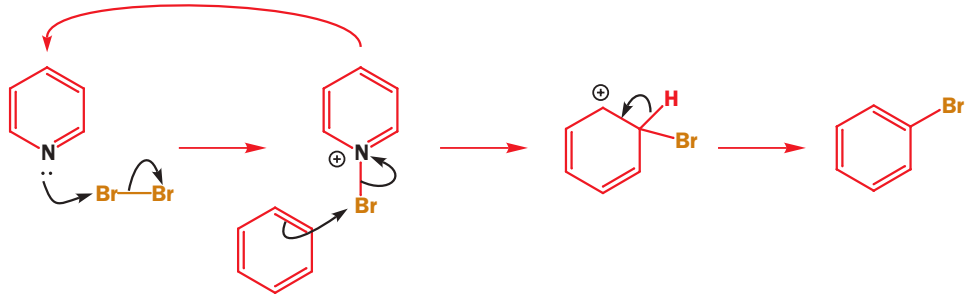
Some applications of pyridine chemistry

One of the simplest ways to brominate benzenes is not to bother with the Lewis acid catalysts recommended in Chapter 22 but just to add liquid bromine to the aromatic compound in the presence of a small amount of pyridine. Only about one mole per cent is needed and even then the reaction has to be cooled to stop it getting out of hand.

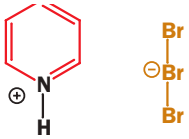


As we have seen, pyridine attacks electrophiles through its nitrogen atom. This produces the reactive species, the *N*-bromo-pyridinium ion, which is attacked by the benzene. Pyridine is a better nucleophile than benzene and a better leaving group than bromide. This is another example of **nucleophilic catalysis**.

Nucleophilic catalysis is discussed on p. 000.

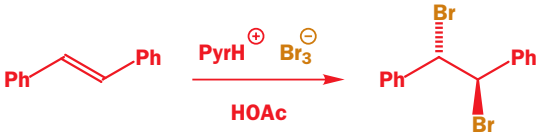


Another way to use pyridine in brominations is to make a stable crystalline compound to replace the dangerous liquid bromine. This compound, known by names such as pyridinium tribromide, is simply a salt of pyridine with the anion Br_3^-. It can be used to brominate reactive compounds such as alkenes (Chapter 20).



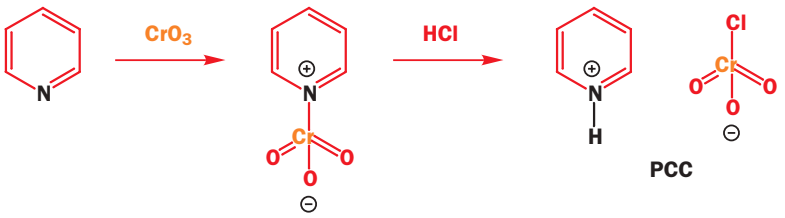
pyridinium tribromide

Both of these methods depend on the lack of reactivity of pyridine's π system towards electrophiles such as bromine. Notice that, in the first case, both benzene and pyridine are

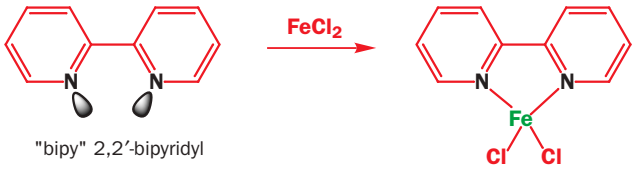


present together. The pyridine attacks bromine only through nitrogen (and reversibly at that) and never through carbon.

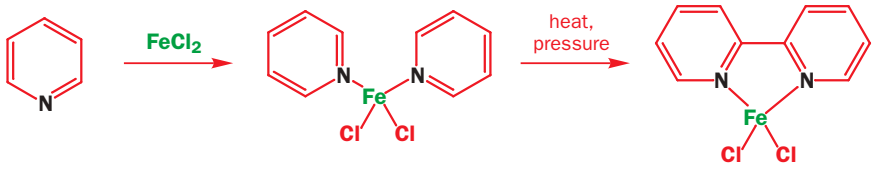
Oxidation of alcohols is normally carried out with Cr(VI) reagents (Chapter 24) but these, like the Jones' reagent ($Na_2Cr_2O_7$ in sulfuric acid), are usually acidic. Some pyridine complexes of Cr(VI) compounds solve this problem by having the pyridinium ion (pK_a 5) as the only acid. The two most famous are 'PDC' (Pyridinium DiChromate) and 'PCC' (Pyridinium Chloro-Chromate). Pyridine forms a complex with CrO_3 but this is liable to burst into flames. Treatment with HCl gives PCC, which is much less dangerous. PCC is particularly useful in the oxidation of primary alcohols to aldehydes as overoxidation is avoided in the only slightly acidic conditions (Chapter 24).



The ability of pyridine to form metal complexes is greatly enhanced in a dimer—the famous ligand 'bipy' or 2,2′-bipyridyl. It is bidentate and because of its 'bite' it is a good ligand for many transition metals but shows a partiality for Fe(II).

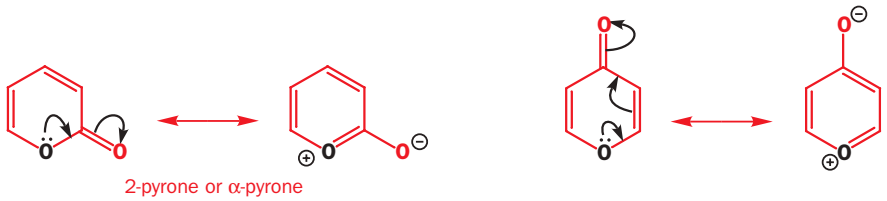


It looks like a rather difficult job to persuade two pyridine rings to join together in this way to form bipy. It is indeed very difficult unless you make things easier by using a reagent that favours the product. And what better than Fe(II) to do the job? ICI manufacture bipy by treating pyridine with $FeCl_2 \cdot 4H_2O$ at high temperatures and high pressures. Only a small proportion of the pyridine is converted to the Fe(II) complex of bipy (about 5%) but the remaining pyridine goes back in the next reaction. This is probably a radical process (Chapter 39) in the coordination sphere of Fe(II).



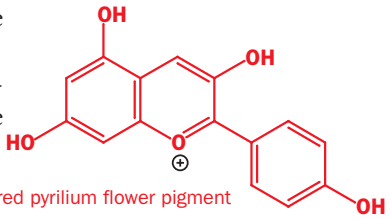
Six-membered aromatic heterocycles can have oxygen in the ring

Though pyridine is overwhelmingly the most important of the six-membered aromatic heterocycles, there are oxygen heterocycles, **pyrones**, that resemble the pyridones. The pyrones are aromatic, though α-pyrone is rather unstable.

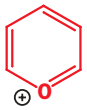


The pyrilium salts are stable aromatic cations and are responsible as metal complexes for some flower colours.

Heterocycles with six-membered rings based on other elements (for example, P) do exist but they are outside the scope of this book.



a red pyrilium flower pigment

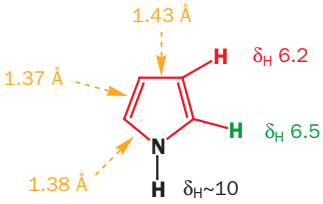


the pyrilium cation

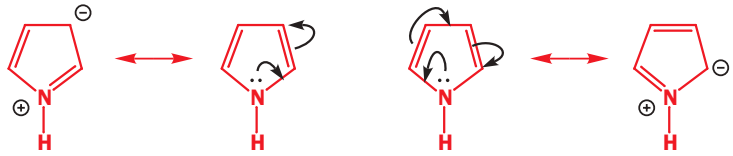
Five-membered heterocycles are good nucleophiles

Just about everything is the other way round with pyrrole. Electrophilic substitution is much easier than it is with benzene—almost too easy in fact—while nucleophilic substitution is more difficult. Pyrrole is not a base nor can it be converted to an *N*-oxide. We need to find out why this is.

The big difference is that the nitrogen lone pair is delocalized round the ring. The NMR spectrum suggests that all the positions in the ring are about equally electron-rich with chemical shifts about 1 p.p.m. smaller than those of benzene. The ring is flat and the bond lengths are very similar, though the bond opposite the nitrogen atom is a bit longer than the others.

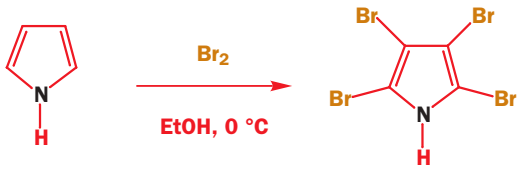


The delocalization of the lone pair can be drawn equally well to any ring atom because of the five-membered ring and we shall soon see the consequences of this. All the delocalization pushes electrons from the nitrogen atom into the ring and we expect the ring to be electron-rich at the expense of the nitrogen atom. The HOMO should go up in energy and the ring become more nucleophilic.

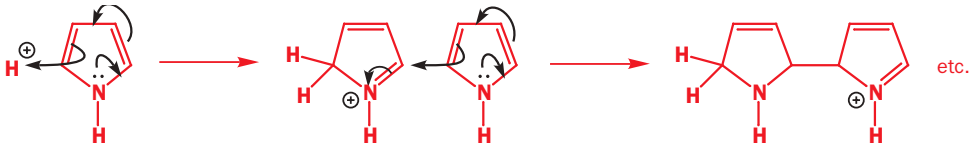


An obvious consequence of this delocalization is the decreased basicity of the nitrogen atom and the increased acidity of the NH group as a whole. In fact, the pK_a of pyrrole acting as a base is about –4 and protonation occurs at carbon. The NH proton can be removed by much weaker bases than those that can remove protons on normal secondary amines.

The nucleophilic nature of the ring means that pyrrole is attacked readily by electrophiles. Reaction with bromine requires no Lewis acid and leads to substitution (confirming the aromaticity of pyrrole) at all four free positions.



This is a fine reaction in its way, but we don't usually want four bromine atoms in a molecule so one problem with pyrrole is to control the reaction to give only monosubstitution. Another problem is that strong acids cannot be used. Though protonation does not occur at nitrogen, it does occur at carbon and the protonated pyrrole then adds another molecule like this.

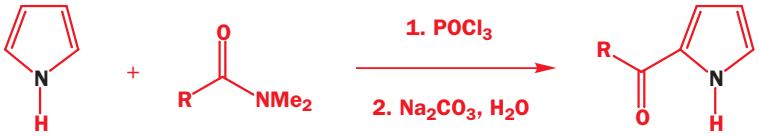


reaction continues to give polymer

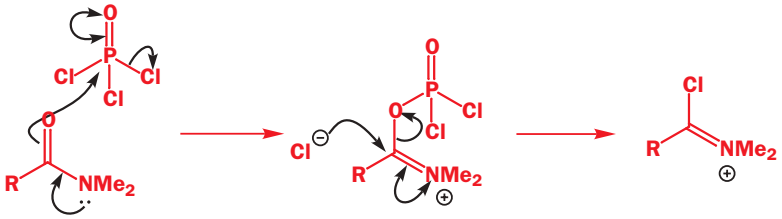
Pyrrole polymerizes!

Strong acids, those such as H_2SO_4 with a pK_a of less than –4, cannot be used without polymerization of pyrrole.

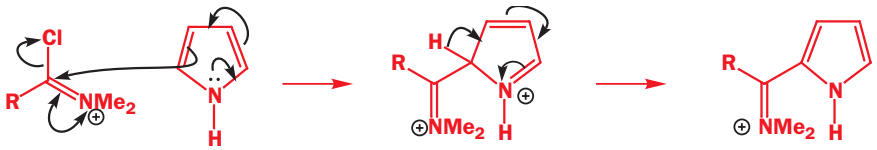
Some reactions can be controlled to give good yields of monosubstituted products. One is the **Vilsmeier reaction** in which a combination of an *N*,*N*-dimethylamide and $POCl_3$ is used to make a carbon electrophile in the absence of strong acid or Lewis acid. It is a substitute for the Friedel–Crafts acylation, and works with aromatic compounds at the more reactive end of the scale (where pyrrole is).



In the first step, the amide reacts with $POCl_3$ which makes off with the amide oxygen atom and replaces it with chlorine. This process would be very unfavourable but for the formation of the strong P–O bond, and is the direct analogy of the chloropyridine-forming reaction you have just seen.

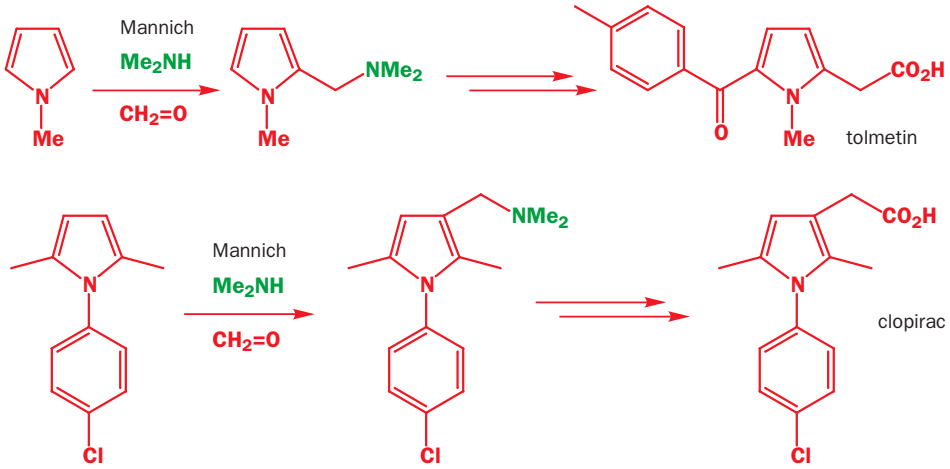


The product from this first step is an iminium cation that reacts with pyrrole to give a more stable iminium salt. The extra stability comes from the conjugation between the pyrrole nitrogen and the iminium group.



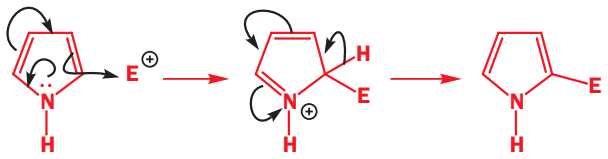
The work-up with aqueous Na_2CO_3 hydrolyses the imine salt and removes any acid formed. This method is particularly useful because it works well with Me_2NCHO (DMF) to add a formyl (CHO) group. This is difficult to do with a conventional Friedel–Crafts reaction.

You may have noticed that the reaction occurred only at the 2-position on pyrrole. Though all positions react with reagents like bromine, more selective reagents usually go for the 2- (or 5-) position and attack the 3- (or 4-) position only if the 2- and 5-positions are blocked. A good example is the Mannich reaction (Chapter 27). In these two examples *N*-methylpyrrole reacts cleanly at the 2-position while the other pyrrole with both 2- and 5-positions blocked by methyl groups reacts cleanly at the 3-position. These reactions are used in the manufacture of the nonsteroidal anti-inflammatory compounds, tolmetin and clopirac.

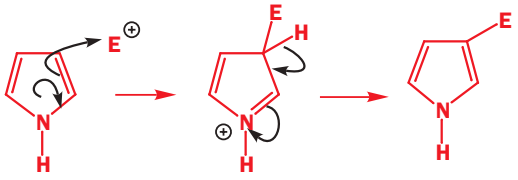


Now we need an explanation. The mechanisms for both 2- and 3-substitutions look good and we will draw both, using a generalized E^+ as the electrophile.

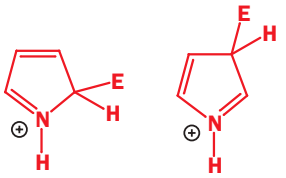
reaction with electrophiles in the 2-position



reaction with electrophiles in the 3-position

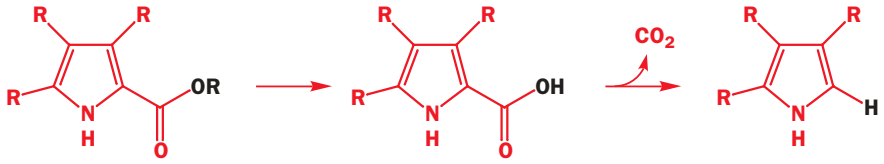


Both mechanisms can occur very readily. Reaction in the 2-position is somewhat better than in the 3-position but the difference is small. Substitution is favoured at *all* positions. Calculations show that the HOMO of pyrrole does indeed have a larger coefficient in the 2-position but that is very much a theoretical chemist's answer, which organic chemists cannot reproduce easily. One way to understand the result is to look at the structure of the intermediates. The intermediate from attack at the 2-position has a linear conjugated system. In both intermediates the two double bonds are, of course, conjugated with each other, but only in the first intermediate are both double bonds conjugated with N^+. The second intermediate is 'cross-conjugated', while the first has a more stable linear conjugated system.

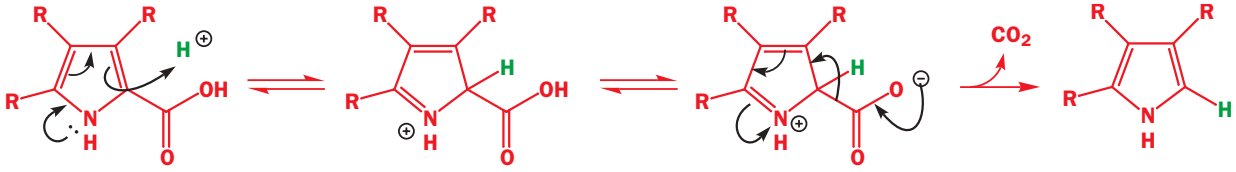


more stable less stable

Since electrophilic substitution on pyrroles occurs so easily, it can be useful to block substitution with a removable substituent. This is usually done with an ester group. Hydrolysis of the ester (this is particularly easy with *t*-butyl esters—see Chapter 24) releases the carboxylic acid, which decarboxylates on heating.

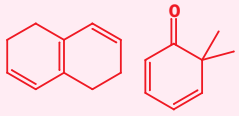


The decarboxylation is a kind of reverse Friedel–Crafts reaction in which the electrophile is a proton (provided by the carboxylic acid itself) and the leaving group is carbon dioxide. The protonation may occur anywhere but it leads to reaction only if it occurs where there is a CO_2H group.

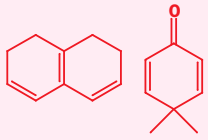


Cross-conjugation explains other differences in stability too. Here are some examples. The linear conjugated systems are more stable than the cross-conjugated ones.

More stable—linear conjugation



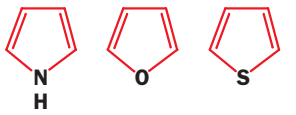
Less stable—cross conjugation



Furan and thiophene are oxygen and sulfur analogues of pyrrole

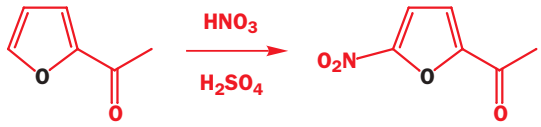
The other simple five-membered heterocycles are furan, with an oxygen atom instead of nitrogen, and thiophene with a sulfur atom. They also undergo electrophilic aromatic substitution very readily, though not so readily as pyrrole. Nitrogen is the most powerful electron donor of the three, oxygen the next, and sulfur the least. Thiophene is very similar to benzene in reactivity.

pyrrole furan thiophene



You may be surprised that thiophene is the least reactive of the three but this is because the p orbital of the lone pair of electrons on sulfur that conjugates with the ring is a 3p orbital rather than the 2p orbital of N or O, so overlap with the 2p orbitals on carbon is less good. Both furan and thiophene undergo more or less normal Friedel–Crafts reactions though the less reactive anhydrides are used instead of acid chlorides, and weaker Lewis acids than $AlCl_3$ are preferred.

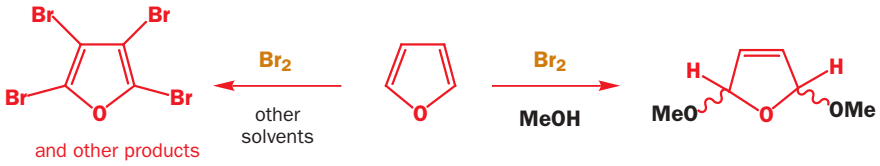
Notice that the regioselectivity is the same as it was with pyrrole—the 2-position is more reactive than the 3-position in both cases. The product ketones are less reactive towards electrophiles than the starting heterocycles and deactivated furans can even be nitrated with the usual reagents used for benzene derivatives. Notice that reaction has occurred at the 5-position in spite of the presence of the ketone. The preference for 2- and 5-substitution is quite marked.



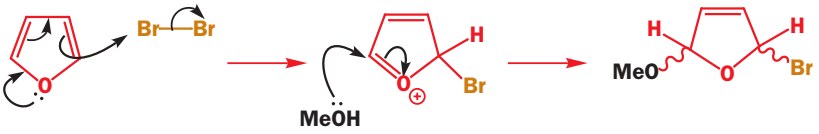
So far, thiophenes and furans look much the same as pyrrole but there are other reactions in which they behave quite differently and we shall now concentrate on those.

Electrophilic addition may be preferred to substitution with furan

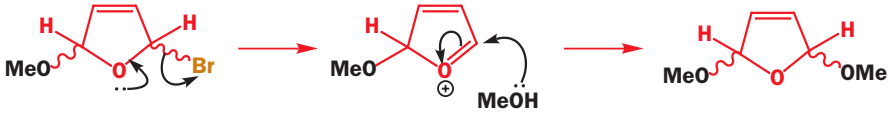
Furan is not very aromatic and if there is the prospect of forming stable bonds such as C–O single bonds by addition, this may be preferred to substitution. A famous example is the reaction of furan with bromine in methanol. In nonhydroxylic solvents, polybromination occurs as expected, but in MeOH no bromine is added at all!



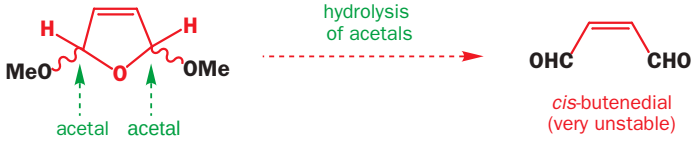
Bromination must start in the usual way, but a molecule of methanol captures the first formed cation in a 1,4-addition to furan.



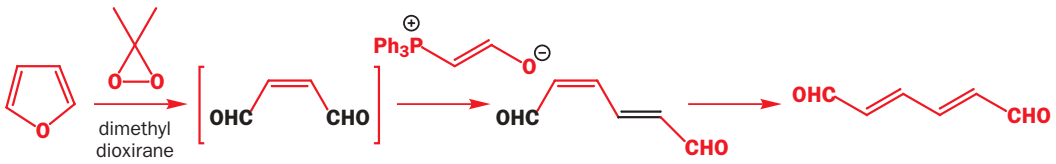
The bromine atom that was originally added is now pushed out by the furan oxygen atom to make a relatively stable conjugated oxonium ion, which adds a second molecule of methanol.



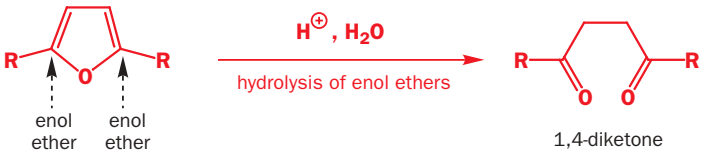
This product conceals an interesting molecule. At each side of the ring we have an acetal, and if we were to hydrolyse the acetals, we would have 'maleic dialdehyde' (*cis*-butenedial)—a molecule that is too unstable to be isolated. The furan derivative may be used in its place.



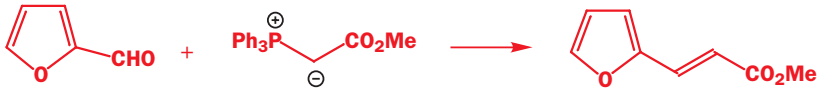
The same 1,4-dialdehyde can be made by oxidizing furan with the mild oxidizing agent dimethyldioxirane, which you met on p. 000. In this sequence, it is trapped in a Wittig reaction to give an *E,Z*-diene, which is easily isomerized to *E,E*.



We can extend this idea of furan being the origin of 1,4-dicarbonyl compounds if we consider that furan is, in fact, an enol ether on both sides of the ring. If these enol ethers were hydrolysed we would get a 1,4-diketone.

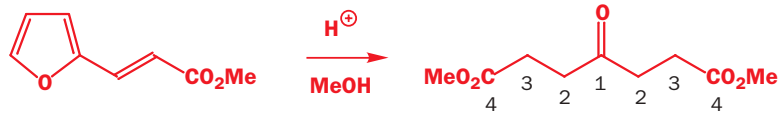


This time the arrow is solid, not dotted, because this reaction really happens. You will discover in the next chapter that furans can also be made from 1,4-diketones so this whole process is reversible. The example we are choosing has other features worth noting. The cheapest starting material containing a furan is furan-2-aldehyde or 'furfural', a by-product of breakfast cereal manufacture. Here it reacts in a typical Wittig process with a stabilized ylid.



furfural stabilized phosphorus ylid

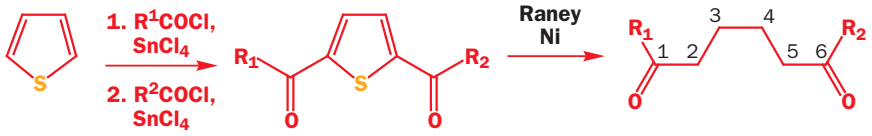
Now comes the interesting step: treatment of this furan with acidic methanol gives a white crystalline compound having two 1,4-dicarbonyl relationships.



▶ You should try to draw a mechanism for this reaction.

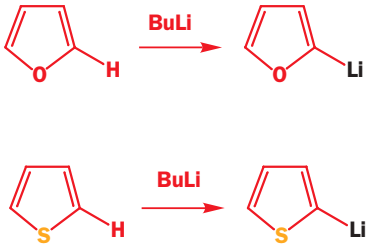
The thiophene ring can also be opened up, but in a very different way. Reductive removal of the sulfur atom with Raney nickel (Chapter 24) reduces not only the C–S bonds but also the double bonds in the ring and we are left with a saturated alkyl chain.

If the reduction follows two Friedel–Crafts reactions on thiophene the product is a 1,6-diketone instead of the 1,4-diketones from furan. Thiophene is well behaved in Friedel–Crafts acylations, and reaction occurs at the 2- and 5-positions unless these are blocked.



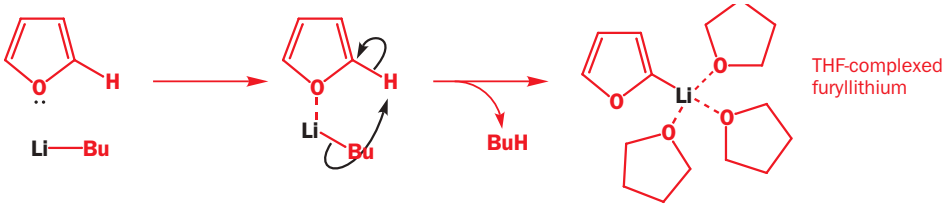
Lithiation of thiophenes and furans

A reaction that furans and thiophenes do particularly well and that fits well with these last two reactions is metallation, particularly lithiation, of a C–H group next to the heteroatom and we will discuss this next. Lithiation of benzene rings (Chapter 9) is carried out by lithium–halogen (Br or I) exchange—a method that works well for heterocycles too as

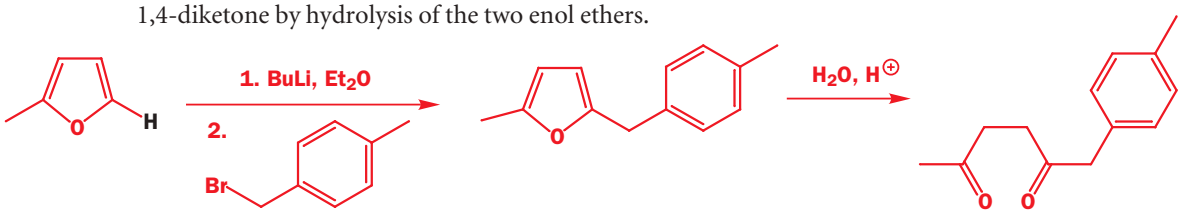


we will see later with pyridine—or by directed ('*ortho*') lithiation of a C–H group next to an activating group such as OMe. With thiophene and furan, the heteroatom in the ring provides the necessary activation.

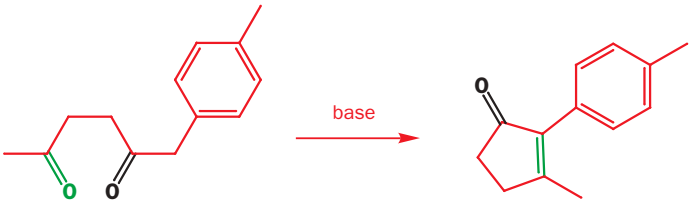
Activation is by coordination of O or S to Li followed by proton removal by the butyl group so that the by-product is gaseous butane. These lithium compounds have a carbon–lithium σ bond and are soluble in organic solvents with the coordination sphere of Li completed by THF molecules.



These lithium compounds are very reactive and will combine with most electrophiles—in this example the organolithium is alkylated by a benzylic halide. Treatment with aqueous acid gives the 1,4-diketone by hydrolysis of the two enol ethers.



Treatment of this diketone with *anhydrous* acid would cause recyclization to the same furan (see Chapter 44) but it can alternatively be cyclized in base by an intramolecular aldol reaction (Chapter 27) to give a cyclopentenone.

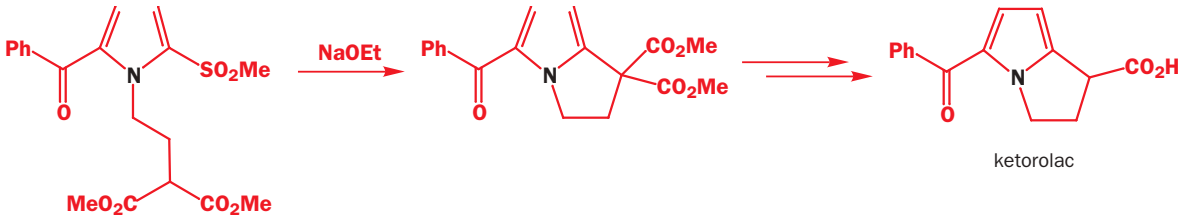


This completes our exploration of chemistry special to thiophene and furan and we now return to all three heterocycles (pyrrole in particular) and look at nucleophilic substitution.

More reactions of five-membered heterocycles

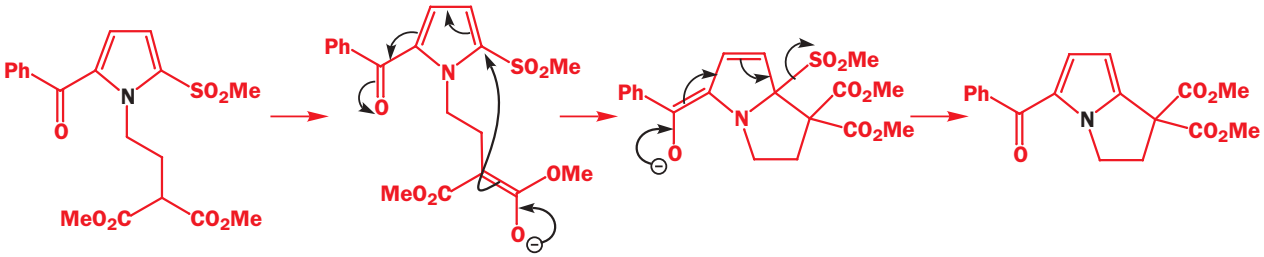
Nucleophilic substitution requires an activating group

Nucleophilic substitution is a relatively rare reaction with pyrrole, thiophene, or furan and requires an activating group such as nitro, carbonyl, or sulfonyl, just as it does with benzene (Chapter 23). Here is an intramolecular example used to make the painkiller ketorolac.



The nucleophile is a stable enolate and the leaving group is a sulfinate anion. An intermediate must be formed in which the negative charge is delocalized on to the carbonyl group on the ring, just as you saw in the benzene ring examples in Chapter 23. Attack occurs at the 2-position because the

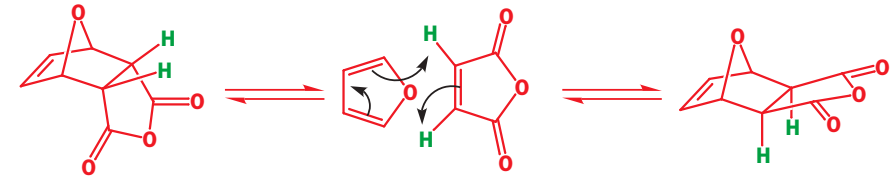
leaving group is there and because the negative charge can be delocalized on to the ketone from that position—there is no inherent preference for attack at the 2- or 5-position.



So far, all of the reactions we have discussed have been variations on reactions of benzene. These heterocycles also do reactions totally unlike those of benzene and we are now going to explore two of them.

Five-membered heterocycles act as dienes in Diels–Alder reactions

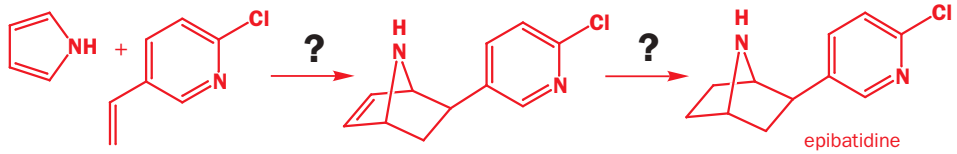
Furan is particularly good at Diels–Alder reactions but it gives the thermodynamic product, the *exo* adduct, because with this aromatic diene the reaction is reversible (Chapter 35).



kinetically preferred
endo adduct

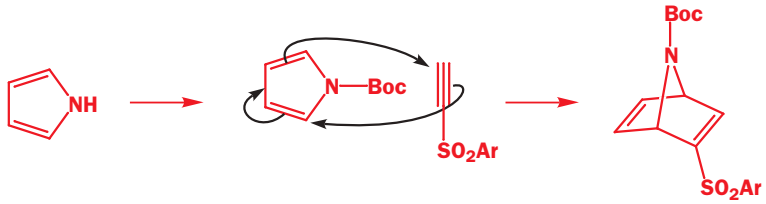
thermodynamically preferred
exo adduct

If pyrrole would do a similar thermodynamically controlled *exo* Diels–Alder reaction with a vinyl pyridine, a short route to the interesting analgesic epibatidine could be imagined, with just a simple reduction of the remaining alkene left to do. The reaction looks promising as the pyridine makes the dienophile electron-deficient and pyrrole is an electron-rich 'diene'.



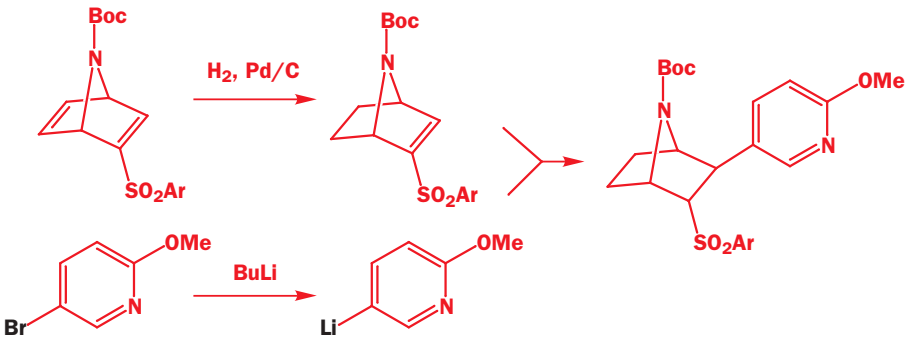
epibatidine

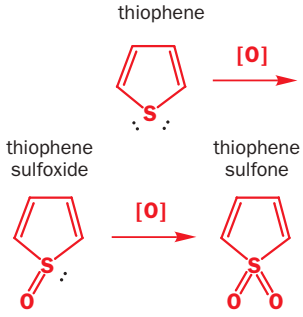
The trouble is that pyrrole will not do this reaction as it is so good at electrophilic substitution. What happens instead is that pyrrole acts as a nucleophile and attacks the electron-deficient alkene. The answer is to make pyrrole less nucleophilic by acylating the nitrogen atom with the famous 'Boc' protecting group (Chapter 24). We will see in the next section how this may be done. A good Diels–Alder reaction then occurs with a alkynyl sulfone.



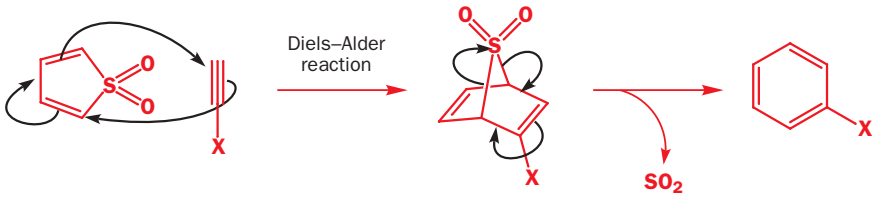
It is then possible to reduce the nonconjugated double bond chemoselectively and add a pyridine nucleophile to the vinyl sulfone. Notice in this step that a lithium derivative can be prepared from a bromopyridine. In general, heterocycles form lithium derivatives rather easily. The skeleton of epibatidine is now complete and you will find some further reactions from the rest of the synthesis in the problems at the end of this chapter.

▶ Epibatidine was discovered in the skin of Ecuadorian frogs in 1992. It is an exceptionally powerful analgesic and works by a different mechanism from that of morphine so there is hope that it will not be addictive. The compound can now be synthesized so there is no need to kill the frogs to get it—indeed, they are a protected species.

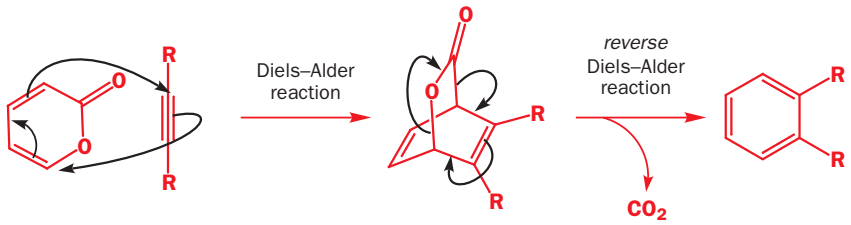




Aromaticity prevents thiophene taking part in Diels–Alder reactions, but oxidation to the sulfone destroys the aromaticity because both lone pairs become involved in bonds to oxygen. The sulfone is unstable and reacts with itself but will also do Diels–Alder reactions with dienophiles. If the dienophile is an alkyne, loss of SO_2 gives a substituted benzene derivative.

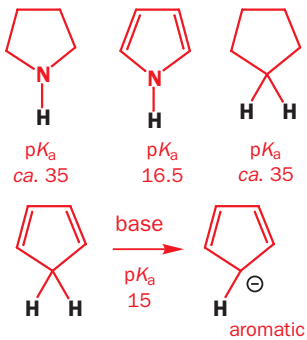


Similar reactions occur with α-pyrones. These are also rather unstable and barely aromatic and they react with alkynes by Diels–Alder reactions followed by reverse Diels–Alder reaction to give benzene derivatives with the loss of CO_2 rather than SO_2.

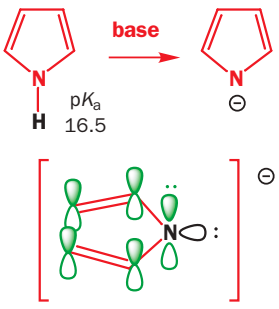


Nitrogen anions can be easily made from pyrrole

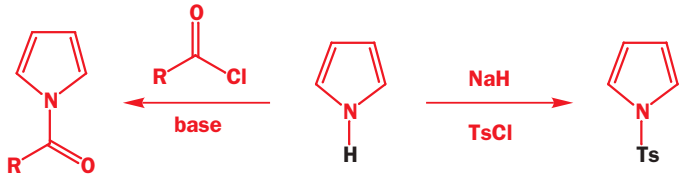
Pyrrole is much more acidic than comparable saturated amines. The pK_a of pyrrolidine is about 35, but pyrrole has a pK_a of 16.5 making it some 10^{23} times more acidic! Pyrrole is about as acidic as a typical alcohol so bases stronger than alkoxides will convert it to its anion. We should not be too surprised at this as the corresponding hydrocarbon, cyclopentadiene, is also extremely acidic with a pK_a of 15. The reason is that the anions are aromatic with six delocalized π electrons. The effect is much greater for cyclopentadiene because the hydrocarbon is not aromatic and much less for pyrrole because it is already aromatic and has less to gain.



In all of the reactions of pyrrole that we have so far seen, new groups have added to the carbon atoms of the ring. The anion of pyrrole is useful because it reacts at nitrogen. The nitrogen atom has two lone pairs of electrons in the anion: one is delocalized around the ring but the other is localized in an sp^2 orbital on nitrogen. This high-energy pair is the new HOMO and this is where the molecule reacts.

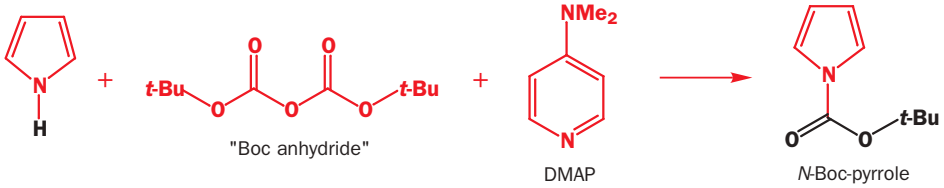


N-acylated derivatives in general can be made in this way. A commonly used base is sodium hydride (NaH) but weaker bases produce enough anion for reaction to occur.



● ***Anions*** **of pyrroles react with electrophiles at the** ***nitrogen*** **atom.**

This is how the *N*-Boc pyrrole was made for use in the synthesis of epibatidine. The base used was the pyridine derivative DMAP, which you met earlier in the chapter. It has a pK_{aH} of 9.7 and so produces small, equilibrating amounts of the anion as well as acting as a nucleophilic catalyst. 'Boc anhydride' is used as the acylating agent.



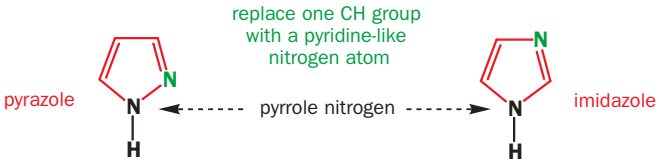
▶ DMAP's pK_{aH} of 9.7 is between those of pyridine (5.5) and tertiary alkyl amines (*ca.* 10) but much closer to the latter.

Anion formation is important in the next main section of this chapter, which is about what happens when we insert more nitrogen atoms into the pyrrole ring.

Five-membered rings with two or more nitrogen atoms

Imidazole

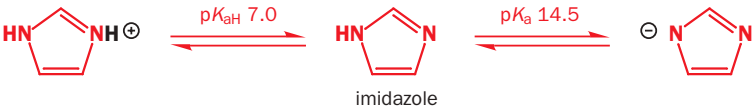
At the beginning of this chapter we imagined adding more nitrogen atoms to the pyrrole ring and noticed then that there were two compounds with two nitrogen atoms: pyrazole and imidazole.

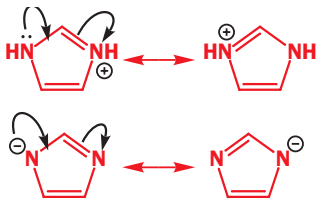


■ The pyrazole ring is present in Viagra (see the beginning of this chapter for the structure) and we will discuss the synthesis of this compound in the next chapter. In this chapter we will concentrate on imidazole.

Only one nitrogen atom in a five-membered ring can contribute two electrons to the aromatic sextet. The other replaces a CH group, has no hydrogen, and is like the nitrogen atom in pyridine. The black nitrogens are the pyrrole-like nitrogens; the green ones are pyridine-like. The lone pairs on the black nitrogens are delocalized round the ring; those on the green nitrogens are localized in sp^2 orbitals on nitrogen. We can expect these compounds to have properties intermediate between those of pyrrole and pyridine.

Imidazole is a stronger base than either pyrrole or pyridine—it has a pK_{aH} of almost exactly 7, meaning that it is 50% protonated in neutral water. It is also more acidic than pyrrole, with a pK_a of 14.5.



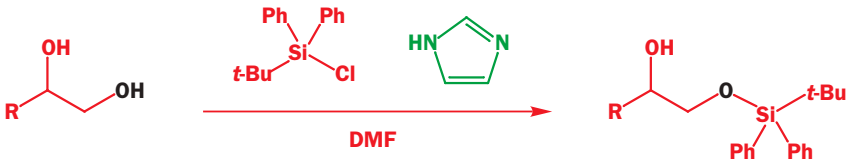


These curious results are a consequence of the 1,3 relationship between the two nitrogen atoms. Both the (protonated) cation and the (deprotonated) anion share the charge equally between the two nitrogen atoms—they are perfectly symmetrical and unusually stable.

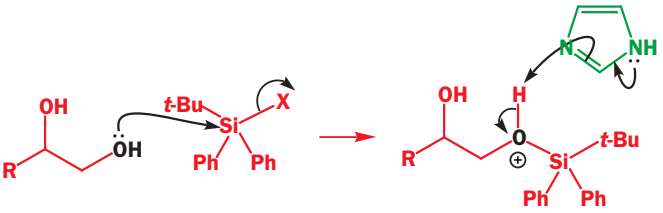
Another way to look at the basicity of imidazole would be to say that both nitrogen atoms can act at once on the proton being attacked. It has to be the pyridine-like nitrogen that actually captures the proton but the pyrrole nitrogen can help by using its delocalized electrons like this.

■ A similar effect accounts for the basicity of DBU and DBN: see p. 000.

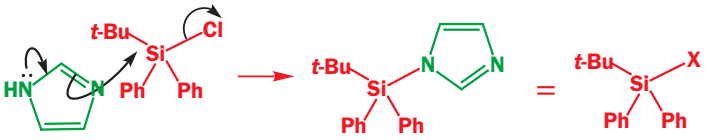
Nature makes use of this property by having imidazole groups attached to proteins in the form of the amino acid histidine and using them as nucleophilic, basic and acidic catalytic groups in enzyme reactions (this will be discussed in Chapters 49 and 50). We use this property in the same way when we add a silyl group to an alcohol. Imidazole is a popular catalyst for these reactions.



A weakly basic catalyst is needed here because we want to discriminate between the primary and secondary alcohols in the diol. Imidazole is too weak (pK_{aH} 7) to remove protons from an alcohol ($pK_a \sim 16$) but it can remove a proton after the OH group has attacked the silicon atom.

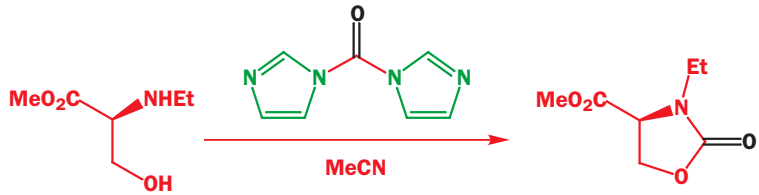


In fact, the imidazole is also a nucleophilic catalyst of this reaction, and the first step is substitution of Cl by imidazole—that is why the leaving group in the last scheme was shown as 'X'. The reaction starts off like this.

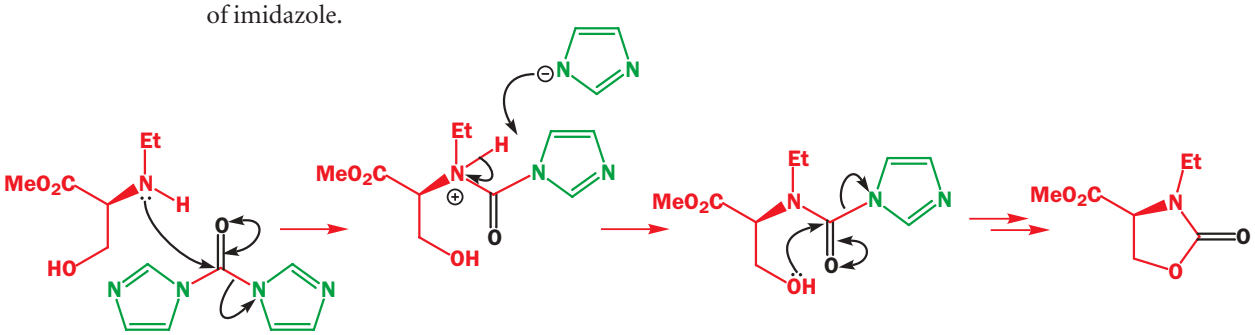


The same idea leads to the use of Carbonyl DiImidazole (CDI) as a double electrophile when we want to link two nucleophiles together by a carbonyl group. Phosgene ($COCl_2$) has been used for this but it is appallingly toxic (it was used in the First World War as a poison gas with dreadful effects). CDI is safer and more controlled. In these reactions imidazole acts (twice) as a leaving group.

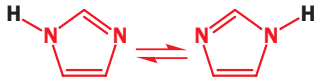
carbonyl diimidazole



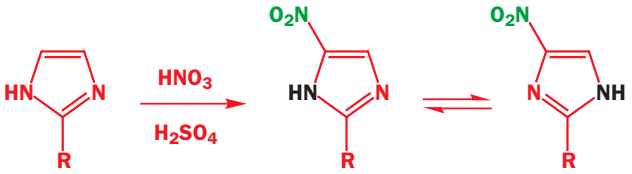
The amino group probably attacks first to displace one imidazole anion, which returns to deprotonate the ammonium salt. The alcohol can then attack intramolecularly displacing the second imidazole anion, which deprotonates the OH group in its turn. The other product is just two molecules of imidazole.



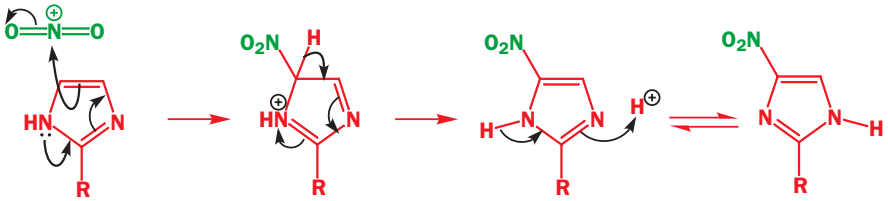
The relationship between the delocalized imidazole anion and imidazole itself is rather like that between an enolate anion and an enol. It will come as no surprise that imidazole tautomerizes rapidly at room temperature in solution. For the parent compound the two tautomers are the same, but with unsymmetrical imidazoles the tautomerism is more interesting. We will explore this question alongside electrophilic aromatic substitution of imidazoles.


two identical tautomers of imidazole

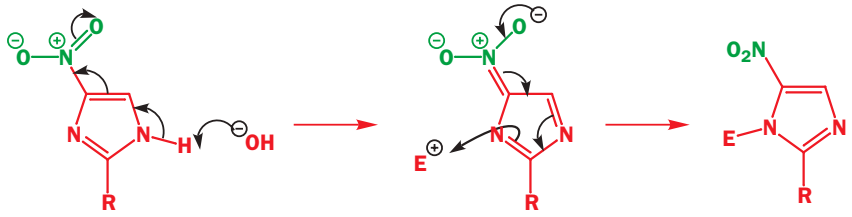
Imidazoles with a substituent between the two nitrogen atoms (position 2) can be nitrated with the usual reagents and the product consists of a mixture of tautomers.



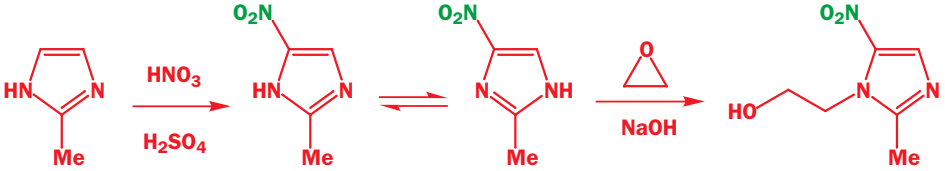
The initial nitration may occur at either of the remaining sites on the ring with the electrons coming from the pyrrole-like nitrogen atom. Tautomerism after nitration gives the mixture.



The tautomerism can be stopped by alkylation at one of the nitrogen atoms. If this is done in basic solution, the anion is an intermediate and the alkyl group adds to the nitrogen atom next to the nitro group. Again, it does not matter from which tautomer the anion is derived—there is only one anion delocalized over both nitrogen atoms and the nitro group. One reason for the formation of this isomer is that it has the linear conjugated system between the pyrrole-like nitrogen and the nitro group (see p. 000).



Important medicinal compounds are made in this way. The antiparasitic metronidazole comes from 2-methyl imidazole by nitration and alkylation with an epoxide in base.

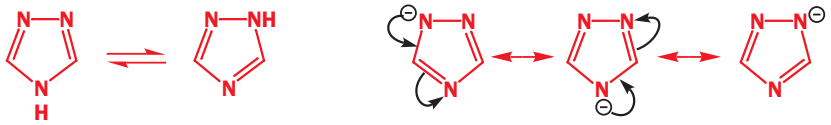


The triazoles

There are two triazoles, and each has one pyrrole-like nitrogen and two pyridine-like nitrogens. Both triazoles have the possibility of tautomerism (in 1,2,3-triazole the tautomers are identical) and both give rise to a single anion.

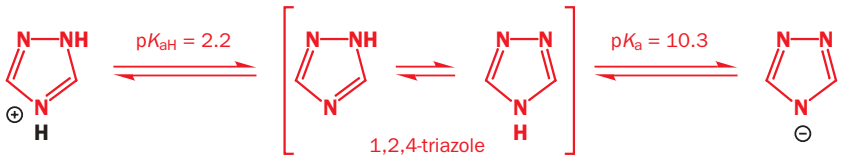

1,2,3-triazole

delocalized anion



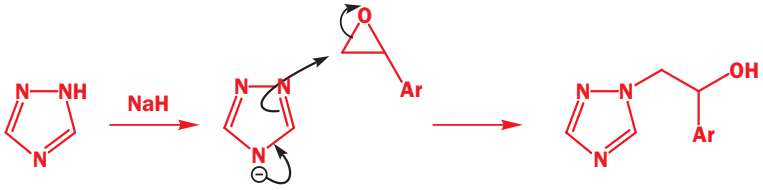
1,2,4-triazole delocalized anion

The 1,2,4-triazole is more important because it is the basis of the best modern agricultural fungicides as well as drugs for fungal diseases in humans. The extra nitrogen atom makes it more like pyridine and so more weakly basic, but it increases its acidity so that the anion is now easy to make.

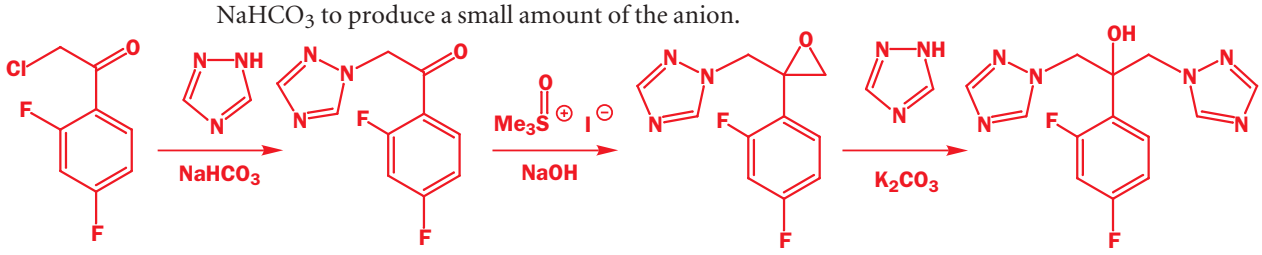


■ This may remind you of the α effect—NH_2NH_2 is more nucleophilic than ammonia because of the two linked nitrogen atoms (see p. 000).

The fungicides are usually made by the addition of the triazole anion to an epoxide or other carbon electrophile. The anion normally reacts at one of the two linked nitrogen atoms (it does not matter which—the product is the same).

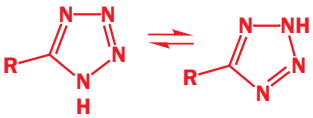


A modern example of an agent used against human fungal infections is Pfizer's fluconazole, which actually contains two triazoles. The first is added as the anion to an α-chloroketone and the second is added to an epoxide made with sulfur ylid chemistry (you will meet this in Chapter 46). Note that weak bases were used to catalyse both of these reactions. Triazole is acidic enough for even $NaHCO_3$ to produce a small amount of the anion.



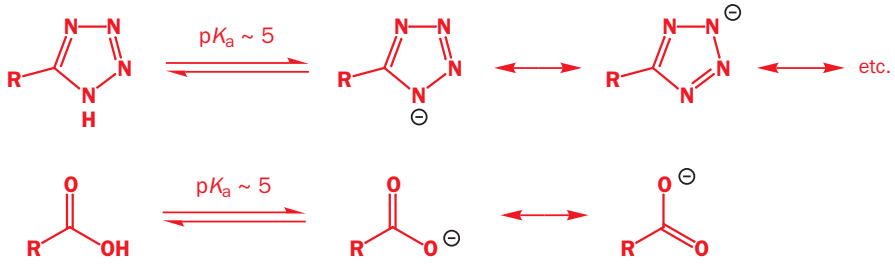
fluconazole

Tetrazole

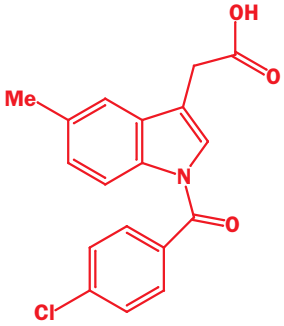


two tautomers of tetrazole

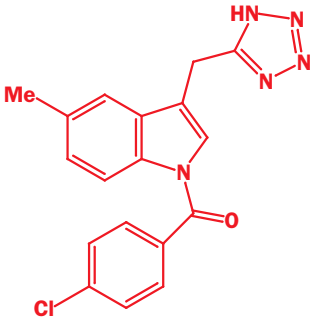
There is only one isomer of tetrazole or of substituted tetrazoles, as there is only one carbon atom in the ring, though there are two tautomers. The main interest in tetrazoles is that they are rather acidic: the pK_a for the loss of the NH proton to form an anion is about 5, essentially the same as that of a carboxylic acid. The anion is delocalized over all four nitrogen atoms (as well as the one carbon atom), and four nitrogen atoms do the work of two oxygen atoms.



Because tetrazoles have similar acidities to those of carboxylic acids, they have been used in drugs as replacements for the CO_2H unit when the carboxylic acid has unsatisfactory properties for human medicine. A simple example is the anti-arthritis drug indomethacin whose carboxylic acid group may be replaced by a tetrazole with no loss of activity.



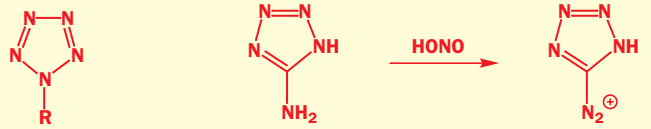
indomethacin



tetrazole substitute for indomethacin

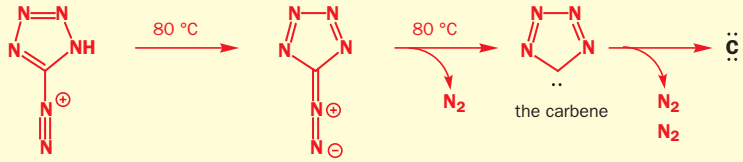
Nitrogen atoms and explosions

Compounds with even two or three nitrogen atoms joined together, such as diazomethane (CH_2N_2) or azides (RN_3), are potentially explosive because they can suddenly give off stable gaseous nitrogen. Compounds with more nitrogen atoms, such as tetrazoles, are likely to be more dangerous and few people have attempted to prepare pentazoles. The limit is reached with diazotetrazole, with the amazing formula CN_6! It is made by diazotization of 5-aminotetrazole, which first gives a diazonium salt.



a pentazole highly explosive! | 5-amino-(1H)-tetrazole | the diazonium salt highly explosive!

The diazonium salt is extremely dangerous: 'It should be emphasised that [the diazonium salt] is extremely explosive and should be handled with great care. We recommend that no more than 0.75 mmol be isolated at one time. Ethereal solutions are somewhat more stable but explosions have occurred after standing at –70 °C for 1 hr.' So much for that, but what about the diazo compound? It is extremely unstable and decomposes to a carbene with loss of one molecule of nitrogen and then loses two more to give...



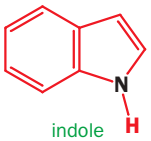
the diazonium salt highly explosive! | the diazo compound highly explosive!

All that is left is a carbon atom and this is one of very few ways to make carbon atoms chemically. The carbon atoms have remarkable reactions and these have been briefly studied, but the hazardous preparation of the starting materials discourages too much research. However, you will see in the next chapter that 1-amino tetrazole is a useful starting material for making an anti-allergic drug.

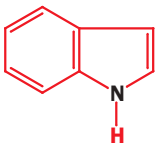
Benzo-fused heterocycles

Indoles are benzo-fused pyrroles

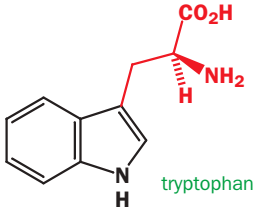
Indomethacin and its tetrazole analogue contain pyrrole rings with benzene rings fused to the side. Such bicyclic heterocyclic structures are called **indoles** and are our next topic. Indole itself has a benzene ring and a pyrrole ring sharing one double bond, or, if you prefer to look at it this way, it is an aromatic system with 10 electrons—eight from four double bonds and the lone pair from the nitrogen atom.



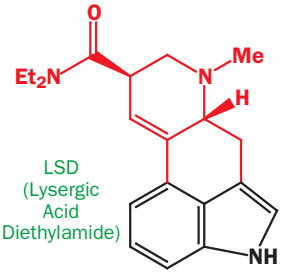
indole



Indole is an important heterocyclic system because it is built into proteins in the form of the amino acid tryptophan (Chapter 49), because it is the basis of important drugs such as indomethacin, and because it provides the skeleton of the **indole alkaloids**—biologically active compounds from plants including strychnine and LSD (alkaloids are discussed in Chapter 51).



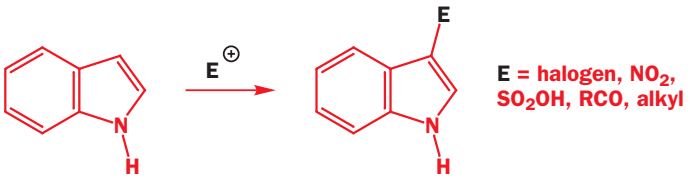
tryptophan



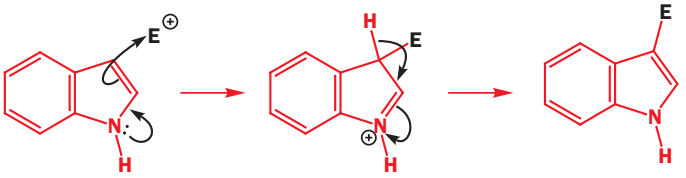
LSD (Lysergic Acid Diethylamide)

▶ Though the first representation is more accurate, you will often see the second used in books and papers.

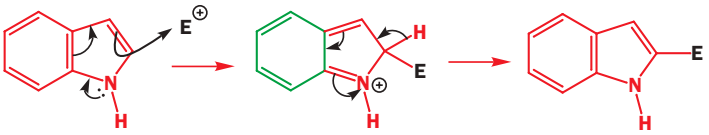
In many ways the chemistry of indole is that of a reactive pyrrole ring with a relatively unreactive benzene ring standing on one side—electrophilic substitution almost always occurs on the pyrrole ring, for example. But indole and pyrrole differ in one important respect. In indole, electrophilic substitution is preferred in the 3-position with almost all reagents. Halogenation, nitration, sulfonation, Friedel–Crafts acylation, and alkylation all occur cleanly at that position.



This is, of course, the reverse of what happens with pyrrole. Why should this be? A simple explanation is that reaction at the 3-position simply involves the rather isolated enamine system in the five-membered ring and does not disturb the aromaticity of the benzene ring.



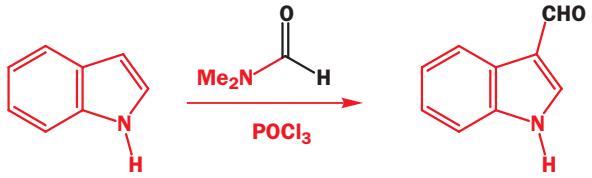
The positive charge in the intermediate is, of course, delocalized round the benzene ring, but it gets its main stabilization from the nitrogen atom. It is not possible to get reaction in the 2-position without seriously disturbing the aromaticity of the benzene ring.



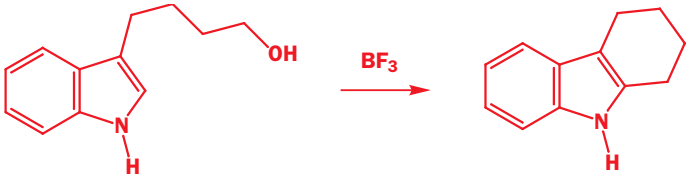
Electrolytic substitution on pyrrole and indole

Pyrrole reacts with electrophiles at all positions but prefers the 2- and 5-positions, while indole much prefers the 3-position.

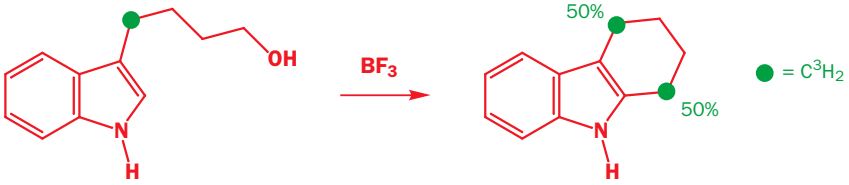
A simple example is the Vilsmeier formylation with DMF and $POCl_3$, showing that indole has similar reactivity, if different regioselectivity, to pyrrole.



If the 3-position is blocked, reaction occurs at the 2-position and this at first seems to suggest that it is all right after all to take the electrons the 'wrong way' round the five-membered ring. This intramolecular Friedel–Crafts alkylation is an example.

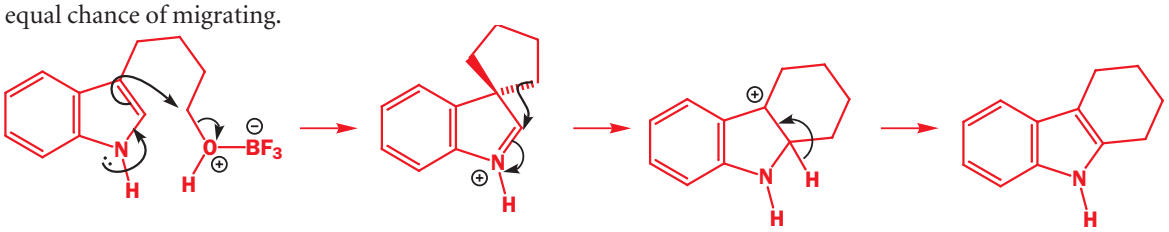


An ingenious experiment showed that this cyclization is not as simple as it seems. If the starting material is labelled with tritium (radioactive ^3H) next to the ring, the product shows exactly 50% of the label where it is expected and 50% where it is not.



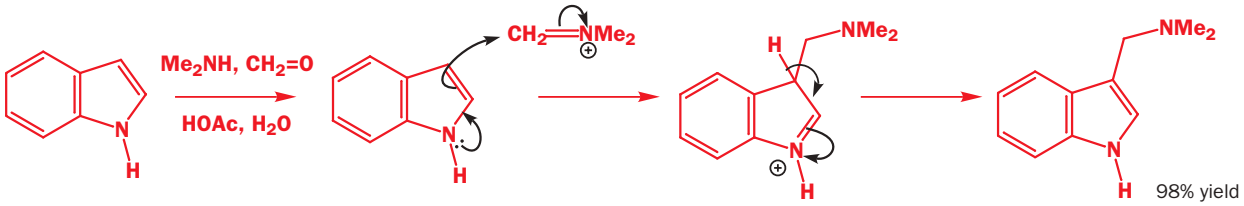
To give this result, the reaction must have a symmetrical intermediate and the obvious candidate

arises from attack at the 3-position. The product is formed from the intermediate *spiro* compound, which has the five-membered ring at right angles to the indole ring—each CH_2 group has an exactly equal chance of migrating.



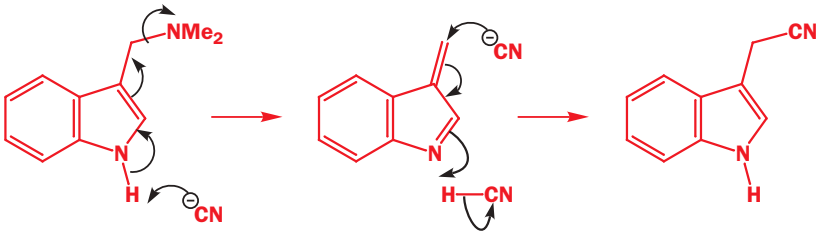
The migration is a pinacol-like rearrangement similar to those in Chapter 37. It is now thought that most substitutions in the 2-position go by this migration route but that some go by direct attack with disruption of the benzene ring.

A good example of indole's 3-position preference is the Mannich reaction, which works as well with indole as it does with pyrrole or furan.



98% yield

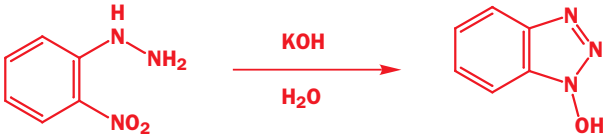
The electron-donating power of the indole and pyrrole nitrogens is never better demonstrated than in the use to which these Mannich bases (the products of the reaction) are put. You may remember that normal Mannich bases can be converted to other compounds by alkylation and substitution (see p. 000). No alkylation is needed here as the indole nitrogen can even expel the Me_2N group when NaCN is around as a base and nucleophile. The reaction is slow and the yield not wonderful but it is amazing that it happens at all. The reaction is even easier with pyrrole derivatives.



All of the five-membered rings we have looked at have their benzo-derivatives but we will concentrate on just one, 1-hydroxybenzotriazole, both because it is an important compound and because we have said little about simple 1,2,3-triazoles.

HOBt is an important reagent in peptide synthesis

1-Hydroxybenzotriazole (HOBt) is a friend in need in the lives of biochemists. It is added to many reactions where an activated ester of one amino acid is combined with the free amino group of another (see Chapter 25 for some examples). It was first made in the nineteenth century by a remarkably simple reaction.



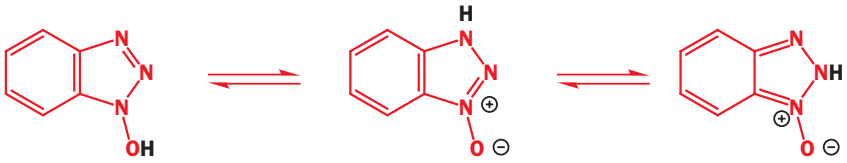
HOBt, 1-hydroxybenzotriazole

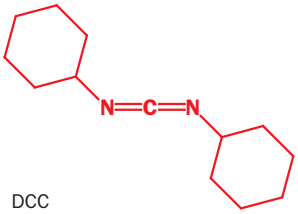
The structure of HOBt appears quite straightforward, except for the unstable N–O single bond, but we can easily draw some other tautomers in which the proton on oxygen—the only one in the

■ The mechanism of this reaction forms one of the problems at the end of the chapter.

■ You met some nitrone chemistry in Chapter 35.

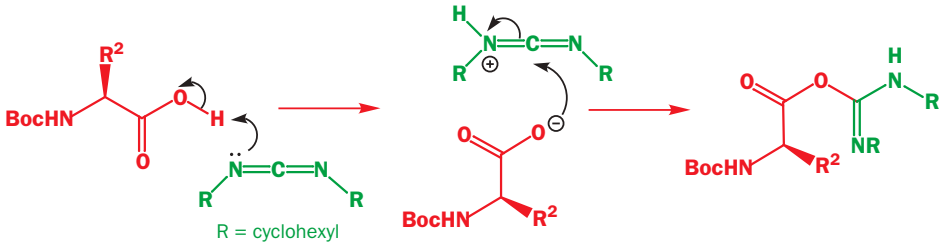
heterocyclic ring—can be placed on some of the nitrogen atoms. These structures are all aromatic, the second and third are nitrones, and the third structure looks less good than the other two.



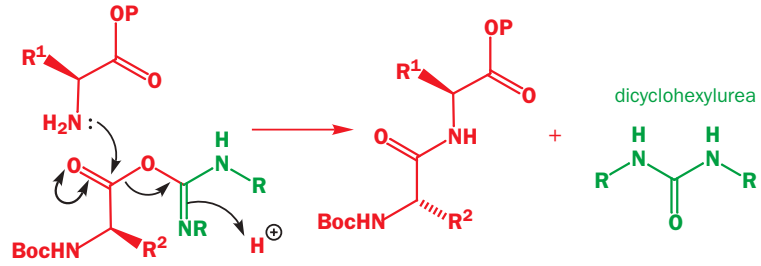


DCC
DiCyclohexylCarbodiimide

HOBt comes into play when amino acids are being coupled together in the lab. The reaction is an amide formation, but in Chapter 25 we mentioned that amino-acyl chlorides cannot be used to make polypeptides—they are too reactive and they lead to side-reactions. Instead, activated amino-esters (with good RO^- leaving groups) are used, such as the phenyl esters of Chapter 25. It even more common to form the activated ester in the coupling reaction, using a **coupling reagent**, the most common being 'DCC', dicyclohexylcarbodiimide. DCC reacts with carboxylic acids like this.

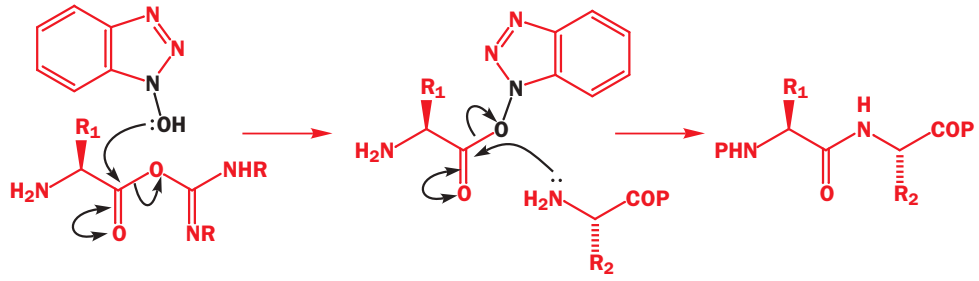


The product ester is activated because substitution with any nucleophile expels this very stable urea as a leaving group.



▶ You saw in Chapter 28 that the most electrophilic carboxylic acid derivatives are also the most enolizable.

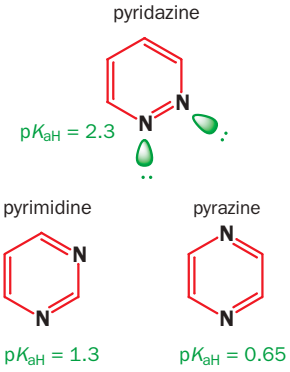
The problem with attacking this ester directly with the amino group of the second amino acid is that some racemization of the active ester is often found. A better method is to have plenty of HOBt around. It intercepts the activated ester first and the new intermediate does not racemize, mostly because the reaction is highly accelerated by the addition of HOBt. The second amino acid, protected on the carboxyl group, attacks the HOBt ester and gives the dipeptide in a very fast reaction without racemization.



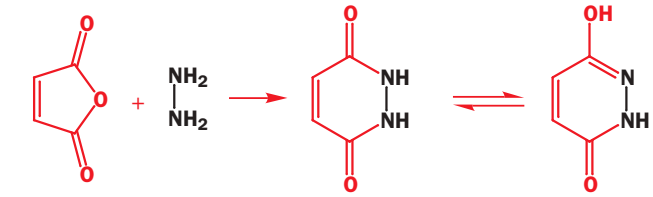
Putting more nitrogen atoms in a six-membered ring

At the beginning of the chapter we mentioned the three six-membered aromatic heterocycles with two nitrogen atoms—pyridazine, pyrimidine, and pyrazine. In these compounds both nitrogen atoms must be of the pyridine sort, with lone pair electrons not delocalized round the ring.

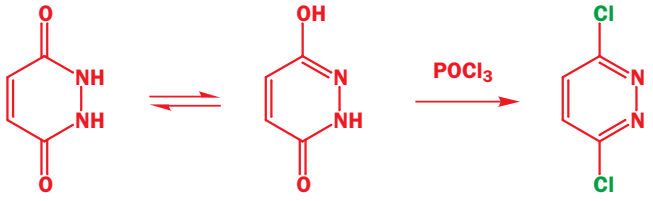
We are going to look at these compounds briefly here. Pyrimidine is more important than either of the others because of its involvement in DNA and RNA—you will find this in Chapter 49. All three compounds are very weak bases—hardly basic at all in fact. Pyridazine is slightly more basic than the other two because the two adjacent lone pairs repel each other and make the molecule more nucleophilic (the α effect again: see p. 000 of Chapter 23).



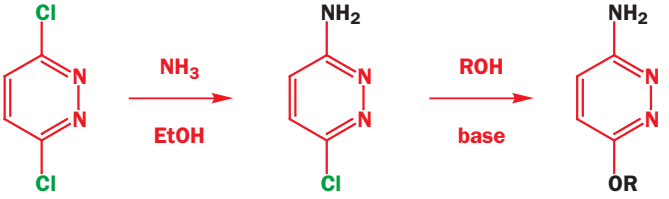
The chemistry of these very electron-deficient rings mostly concerns nucleophilic attack and displacement of leaving groups such as Cl by nucleophiles such as alcohols and amines. To introduce this subject we need to take one heterocyclic synthesis at this point, though these are properly the subject of the next chapter. The compound 'maleic hydrazide' has been known for some time because it is easily formed when hydrazine is acylated twice by maleic anhydride.



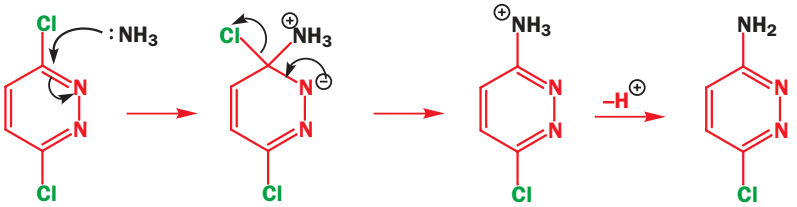
The compound actually prefers to exist as the second tautomer, which is 'more aromatic'. Reaction with $POCl_3$ in the way we have seen for pyridine gives the undoubtedly aromatic pyridazine dichloride.



Now we come to the point. Each of these chlorides can be displaced in turn with an oxygen or nitrogen nucleophile. Only one chloride is displaced in the first reaction, if that is required, and then the second can be displaced with a different nucleophile (see reaction on the right).

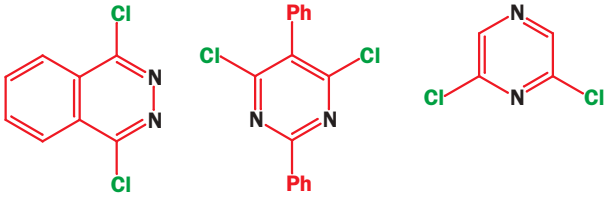


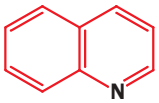
How is this possible? The mechanism of the reactions is addition to the pyridazine ring followed by loss of the leaving group, so the first reaction must go like this.

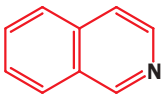


When the second nucleophile attacks it is forced to attack a less electrophilic ring. An electron-withdrawing group (Cl) has been replaced by a strongly electron-donating group (NH_2) so the rate-determining step, the addition of the nucleophile, is slower.

The same principle applies to other easily made symmetrical dichloro derivatives of these rings and their benzo-analogues. The nitrogen atoms can be related 1,2, 1,3, or 1,4 as in the examples alongside. The first two are used to link the quinine-derived ligands required for the Sharpless asymmetric dihydroxylation, which will be described in Chapter 45.




quinoline

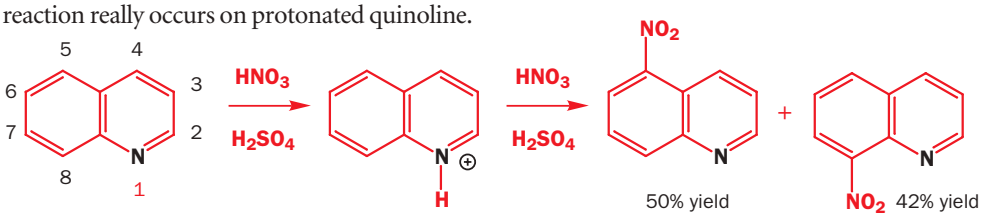

isoquinoline

Fusing rings to pyridines : quinolines and isoquinolines

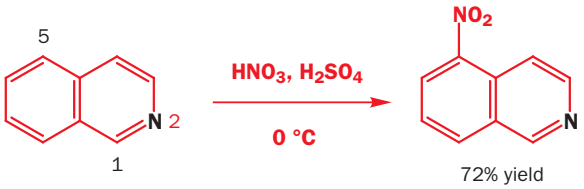
A benzene ring can be fused on to the pyridine ring in two ways giving the important heterocycles quinoline, with the nitrogen atom next to the benzene ring, and isoquinoline, with the nitrogen atom in the other possible position.

Quinoline forms part of quinine (structure at the head of this chapter) and isoquinoline forms the central skeleton of the isoquinoline alkaloids, which we will discuss at some length in Chapter 51. In this chapter we need not say much about quinoline because it behaves rather as you would expect—its chemistry is a mixture of that of benzene and pyridine. Electrophilic substitution favours the benzene ring and nucleophilic substitution favours the pyridine ring. So nitration of quinoline gives two products—the 5-nitroquinolines and the 8-nitroquinolines—in about equal quantities (though you will realize that the reaction really occurs on protonated quinoline.

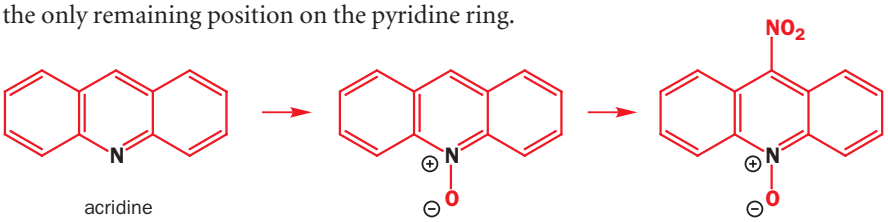
▶ Quinoline numbering, for nomenclature purposes, is shown on this structure.



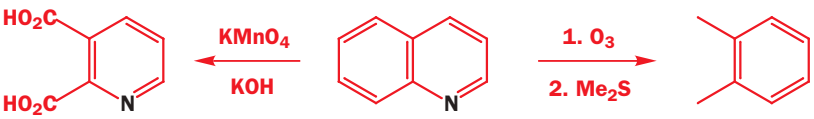
This is obviously rather unsatisfactory but nitration is actually one of the better behaved reactions. Chlorination gives ten products (at least!), of which no fewer than five are chlorinated quinolines of various structures. The nitration of isoquinoline is rather better behaved, giving 72% of one isomer (5-nitroisoquinoline) at 0 °C.



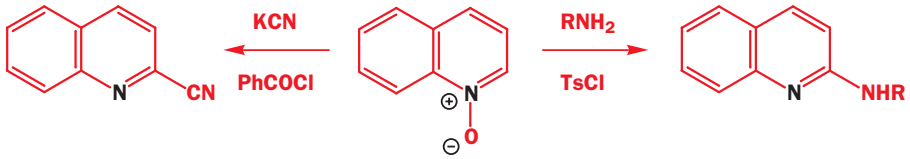
To get reaction on the pyridine ring, the *N*-oxide can be used as with pyridine itself. A good example is acridine, with two benzene rings, which gives four nitration products, all on the benzene rings. Its *N*-oxide, on the other hand, gives just one product in good yield—nitration takes place at the only remaining position on the pyridine ring.



In general, these reactions are of not much use and most substituents are put into quinolines during ring synthesis from simple precursors as we will explain in the next chapter. There are a couple of quinoline reactions that are unusual and interesting. Vigorous oxidation goes for the more electron-rich ring, the benzene ring, and destroys it leaving pyridine rings with carbonyl groups in the 2- and 3-positions.

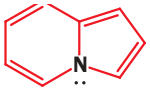


A particularly interesting nucleophilic substitution occurs when quinoline *N*-oxide is treated with acylating agents in the presence of nucleophiles. These two examples show that nucleophilic substitution occurs in the 2-position and you may compare these reactions with those of pyridine *N*-oxide. The mechanism is similar.



In considering quinolines and indoles with their fused rings we kept the benzene and heterocyclic rings separate. Yet there is a way in which they can be combined more intimately, and that is to have a nitrogen atom at a ring junction.

A nitrogen atom can be at a ring junction



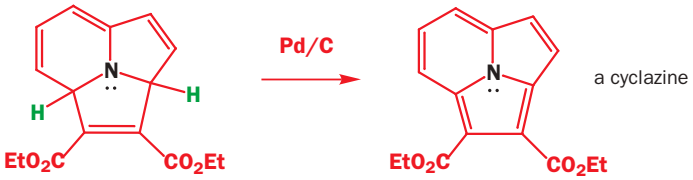
indolizine

It has to be a pyrrole-type nitrogen as it must have three σ bonds, so the lone pair must be in a p orbital. This means that one of the rings must be five-membered and the simplest member of this interesting class is called **indolizine**—it has pyridine and pyrrole rings fused together along a C–N bond.

If you examine this structure you will see that there is definitely a pyrrole ring but that the pyridine ring is not all there. Of course, the lone pair and the π electrons are all delocalized but this system, unlike indole and quinoline, is much better regarded as a ten-electron outer ring than as two six-electron rings joined together.

Indolizine reacts with electrophiles on the five-membered rings by substitution reactions as expected but it has one special reaction that leads dramatically to a more complex aromatic system. It does a cycloaddition with diethyl acetylenedicarboxylate to give a tricyclic molecule.

The dienophile is the usual sort of unsaturated carbonyl compound—but count the electrons used from the indolizine. The nitrogen lone pair is not used but all the other eight are, so this is a most unusual [2 + 8] cycloaddition. The first formed product is not aromatic (it is not fully conjugated) but it can be dehydrogenated with palladium to make a **cyclazine**.



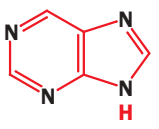
a cyclazine

▶ Notice that this is the reverse of a hydrogenation: the catalyst is the same but H_2 is lost, not gained.

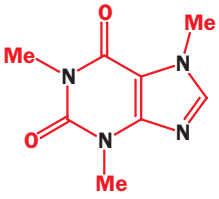
Now count the electrons in the cyclazine—there are ten electrons round the outer edge and the nitrogen lone pair is not part of the aromatic system. Cyclazines have NMR spectra and reactions that suggest they are aromatic.

Fused rings with more than one nitrogen

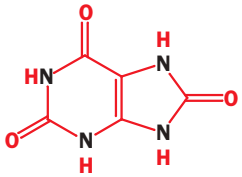
It is easily possible to continue to insert nitrogen atoms into fused ring systems and some important compounds belong to these groups. The **purines** are part of DNA and RNA and are treated in Chapter 49, but simple purines play an important part in our lives. Coffee and tea owe their stimulant properties to caffeine, a simple trimethyl purine derivative. It has an imidazole ring fused to a pyrimidine ring and is aromatic in spite of the two carbonyl groups.



purine

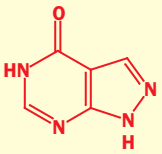


caffeine



uric acid

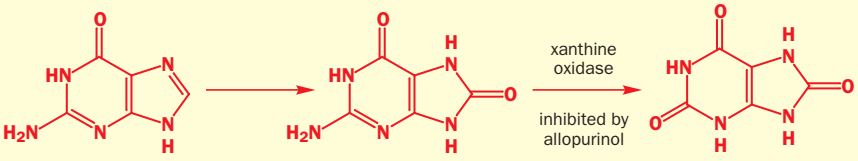
Uric acid, gout, and allopurinol



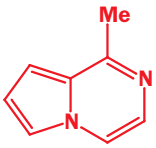
allopurinol

Another purine, uric acid, occurs widely in nature—it is used by birds, and to some extent by humans, as a way to excrete excess nitrogen—but it causes much distress in humans when crystalline uric acid is deposited in joints. We call the pain 'gout' and it isn't funny. The solution is a specific inhibitor of the enzyme producing uric acid and it is no surprise that a compound closely resembling uric acid, allopurinol, is the best.

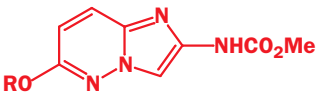
Two of the carbonyl groups have gone and the imidazole ring has been replaced by a pyrazole ring. Purines from DNA are degraded in the body to xanthine, which is oxidized to uric acid. Allopurinol binds to the enzyme xanthine oxidase but inactivates it by not reacting. In fact it imitates not uric acid but the true substrate xanthine in a competitive fashion. This enzyme plays a minor part in human metabolism so inhibiting it is not serious—it just prevents overproduction of uric acid.



guanine xanthine uric acid



smell of roast meat



useful medicinal compounds

Other fused heterocycles have very attractive flavour and odour properties. Pyrazines, in general, are important in many strong food flavours: a fused pyrazine with a ring junction nitrogen atom is one of the most important components in the smell of roast meat. You can read about the simple pyrazine that provides green peppers with their flavour in the Box on the next page.

Finally, the compounds in the margin form a medicinally important group of molecules, which includes antitumour compounds for humans and anthelmintics (compounds that get rid of parasitic worms) for animals. They are derived from a 6/5 fused aromatic ring system that resembles the ten-electron system of the indolizine ring system but has three nitrogen atoms.

All this multiple heteroatom insertion is possible only with nitrogen and we need to look briefly at what happens when we combine nitrogen with oxygen or in heterocycles.

Heterocycles can have many nitrogens but only one sulfur or oxygen in any ring

oxazole

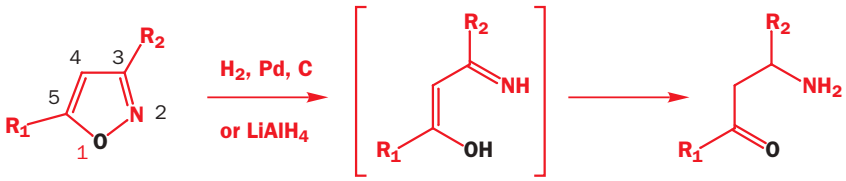
thiazole

isoxazole

isothiazole

A neutral oxygen or sulfur atom can have only two bonds and so it can never be like the nitrogen atom in pyridine—it can only be like the nitrogen atom in pyrrole. We can put as many pyridine-like nitrogens as we like in an aromatic ring, but never more than one pyrrole-like nitrogen. Similarly, we can put only one oxygen or sulfur atom in an aromatic ring. The simplest examples are oxazoles and thiazoles and their less stable isomers.

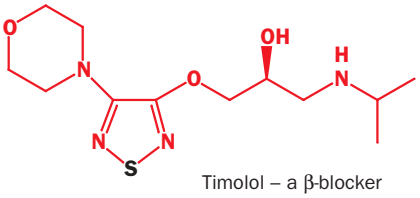
The instability of the 'iso-' compounds comes from the weak O–N or S–N bond. These bonds can be cleaved by reducing agents, which then usually reduce the remaining functional groups further. The first product from reduction of the N–O bond is an unstable imino-enol. The enol tautomerizes to the ketone and the imine may be reduced further to the amine. We used this sort of chemistry on the products of 1,3-dipolar cycloadditions in Chapter 35 and **isoxazoles** are usually formed by such reactions.



3,5-disubstituted isoxazole

Such heterocycles with even more nitrogen atoms exist but are relatively unimportant and we shall mention just one, the 1,2,5-thiadiazole, because it is part of a useful drug, timolol.

1,2,5-thiadiazole



Timolol – a β-blocker

▶ Timolol is a β-blocker that blocks one action of adrenaline (epinephrine) and keeps heart disease at bay by counteracting high blood pressure.

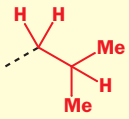
The flavour of green peppers

As a review of spectroscopy we shall describe the discovery of the compound responsible for the flavour of green peppers. This powerful compound was isolated from the oil of the green pepper (*Capsicum annuum* var. *grossum*). The oil makes up about 0.0001% of the mass of the peppers and the main pepper flavour comes from one compound which is 30% of the oil. It had an even molecular ion at 166 and looks like a compound without nitrogen, perhaps $C_{11}H_{18}O$. But a high-resolution mass spectrum revealed that M^+ was actually 166.1102 which corresponds almost exactly to $C_9H_{14}N_2O$ (166.1106).

The IR had no OH, NH, or C=O peaks, and the proton NMR looked like this.

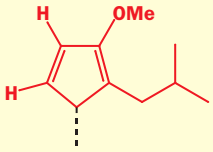
δ_H, p.p.m.	Integral	Shape	*J*, Hz	Comments
0.91	6H	d	6.7	**Me$_2$**CH-
1.1–2.4	1H	m	?	
2.61	2H	d	7.0	**CH$_2$**CH-
3.91	3H	s	—	-O**Me**?
7.80	1H	d	2.4	aromatic
7.93	1H	d	2.4	aromatic

The 'CH' feature in the Me_2CH and CH_2CH signals must be the same CH and it must be the signal at 1.1–2.4 p.p.m. described as a 'multiplet' as it is the only one showing enough coupling. It will be a septuplet of triplets, that is, 21 lines. We can easily reconstruct the aliphatic part of the molecule because it has two methyl groups and a CH_2 group joined to the same CH group.

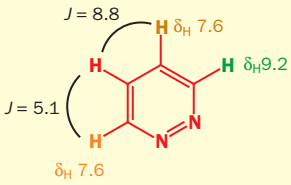


side chain of green pepper flavour compound

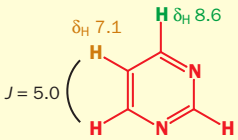
We also have an OMe group (only oxygen is electronegative enough to take a methyl group to nearly 4 p.p.m.). This adds up to $C_5H_{12}O$. What is left? Only $C_4H_2N_2$—and no clue yet as to the nitrogen functionality. We also have an aromatic ring that must have nitrogen in it (because there are only five carbon atoms—not enough for a benzene ring!) and the coupling constant between the two aromatic hydrogens is 2.4 Hz. So could we perhaps have a pyrrole ring? Well, no, and for two reasons. If we try and construct such a molecule, we can't fit in the last nitrogen! If we put it on the end of the dotted line, it would have to be an NH_2 group, and there isn't one.



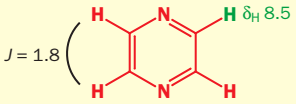
A better reason is that the chemical shifts are all wrong. The protons on an electron-rich pyrrole ring come at around 6–6.5 p.p.m., upfield from benzene (7.27 p.p.m.). But these protons are at 7.8–8.0 p.p.m., downfield from benzene. We have a deshielded (electron-poor) ring, not a shielded (electron-rich) ring. From what you now know of heterocyclic chemistry, the ring must be a six-membered one, and we must put both nitrogen atoms in the ring. There are three ways to do this.



pyridazine (1,2-nitrogens)

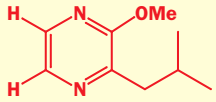


pyrimidine (1,3-nitrogens)



pyrazine (1,4-nitrogens)

The small coupling constant really fits the pyrazine alone and the chemical shifts are about right for that molecule too, though not as far downfield. But we have a MeO group on the ring feeding electrons into the aromatic system and that will increase the shielding slightly and move the protons upfield. This gives us a unique structure.

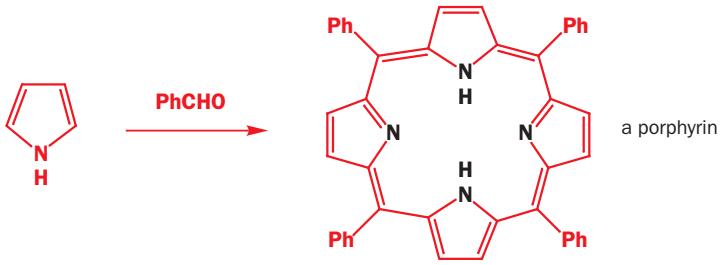


correct structure of the main flavour compound from green peppers

There is only one way to be sure and that is to make this compound and see if it is the same as the natural product in all respects including biological activity. The investigators did this but then wished that they hadn't! The structure was indeed correct but the biological activity—the smell of green peppers—was so intense that they had to seal up the laboratory where the work was done as no one would work there. Human beings can detect 2 parts in 10^{12} of this compound in water.

There are thousands more heterocycles out there

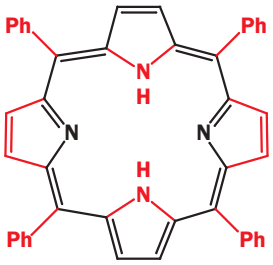
But we're not going to discuss them and we hope you're grateful. In fact, it's about time to stop, and we shall leave you with a hint of the complexity that is possible. If pyrrole is combined with benzaldehyde a good yield of a highly coloured crystalline compound is formed. This is a **porphyrin**.



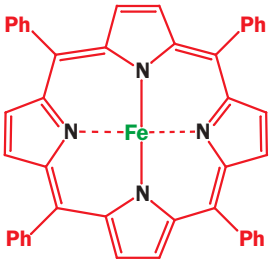
a porphyrin

Now, what about this ring system—is it aromatic? It's certainly highly delocalized and your answer to the question clearly depends on whether you include the nitrogen electrons or not. In fact, if you ignore the pyrrole-like nitrogen atoms but include the pyridine-like nitrogens and weave round the periphery, you have nine double bonds and hence 18 electrons—a $4n + 2$ number. Most people agree that these compounds are aromatic.

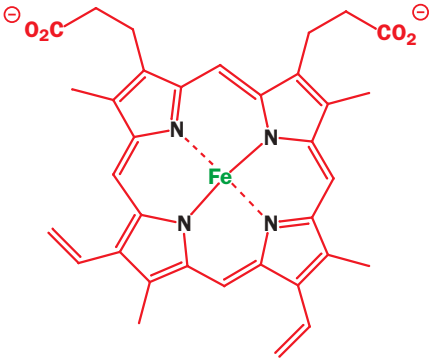
They are also more than curiosities. The space in the middle with the four inward-pointing nitrogen atoms is just right for complex formation with divalent metals such as Fe(II). With more varied substituents, this structure forms the reactive part of haemoglobin, and the iron atom in the middle transports the oxygen in blood.



the 18 π-electron system of a porphyrin

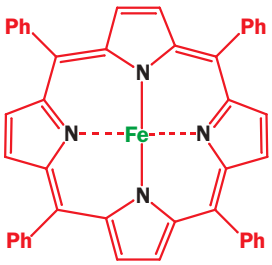


an iron–porphyrin complex

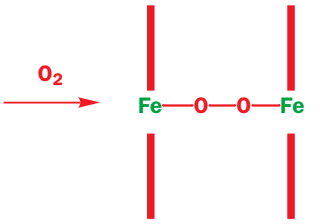


the iron porphyrin in haemoglobin

Iron prefers to be octahedral with six bonds around it and in one of these spare places in haemoglobin that is occupied by oxygen. If you try and make an oxygen complex of the simple porphyrin with four phenyl groups around the edge you get a sandwich dimer that oxidizes itself.

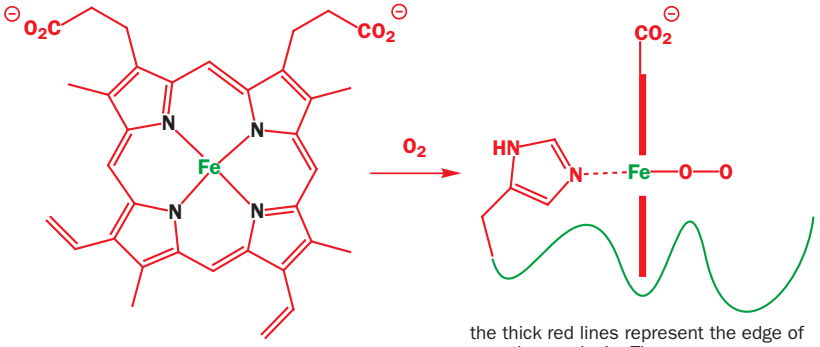


an iron–porphyrin complex



porphyrin rings side-on

The porphyrin in blood avoids this problem by having another heterocycle to hand. Haemoglobin consists of the flat porphyrin bound to a protein by coordination between an imidazole in the protein (a histidine residue: see Chapter 49) and the iron atom. This leaves one face free to bind oxygen and makes the molecule far too big to dimerize.

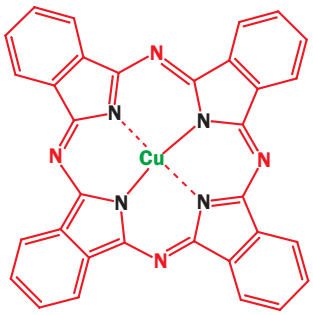


the iron porphyrin in haemoglobin

the thick red lines represent the edge of the porphyrin. The green curve represents the protein

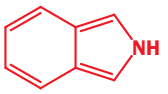
Haem–metal complexes are strongly coloured—the iron complex is literally blood red. Some related compounds provide the familiar blue and green pigments used to colour plastic shopping bags. These are the phthalocyanine–metal complexes, which provide intense pigments in these ranges. The basic ring system resembles a porphyrin.

a simple phthalocyanine

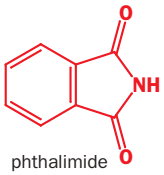


a phthalocyanine–copper complex

The differences are the four extra nitrogen atoms between the rings and the fused benzene rings. These compounds are derivatives of phthalimide, an isoindole derivative that has a nonaromatic five-membered ring. The metal most commonly used with phthalocyanines is Cu(II), and the range of colours is achieved by halogenating the benzene rings. The biggest producer is ICI at Grangemouth in Scotland where they do the halogenation and the phthalocyanine formation to make their range of Procyon™ dyes.

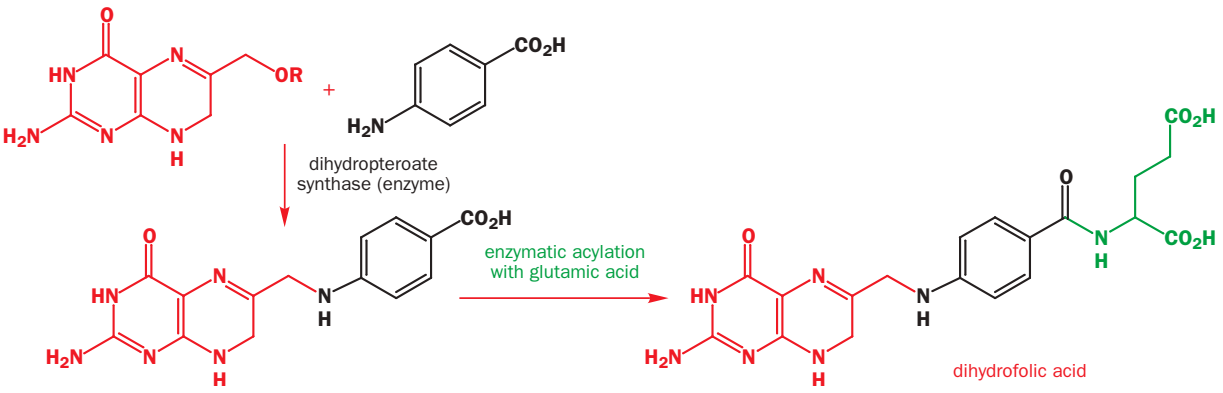


unstable isoindole



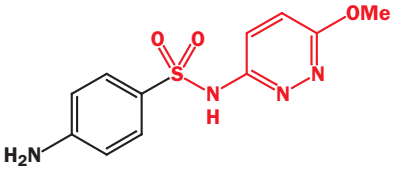
phthalimide

Some heterocycles are simple, some very complex, but we cannot live without them. We shall end this chapter with a wonderful story of heterocyclic chemistry at work. Folic acid is much in the news today as a vitamin that is particularly important for pregnant mothers, but that is involved in the metabolism of all living things. Folic acid is built up in nature from three pieces: a heterocyclic starting material (red), *p*-aminobenzoic acid (black) and the amino acid glutamic acid (brown). Here you see the precursor, dihydrofolic acid.

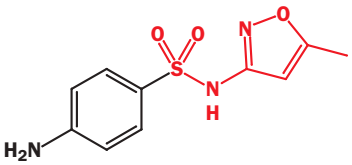


dihydrofolic acid

Although folic acid is vital for human health, we don't have the enzymes to make it: it's a vitamin, which means we must take it in our diet or we die. Bacteria, on the other hand, do make folic acid. This is very useful, because it means that if we inhibit the enzymes of folic acid synthesis we can kill bacteria but we cannot possibly harm ourselves as we don't have those enzymes. The sulfa drugs, such as sulfamethoxypyridazine or sulfamethoxazole, imitate *p*-aminobenzoic acid and inhibit the enzyme dihydropteroate synthase. Each has a new heterocyclic system added to the sulfonamide part of the drug.

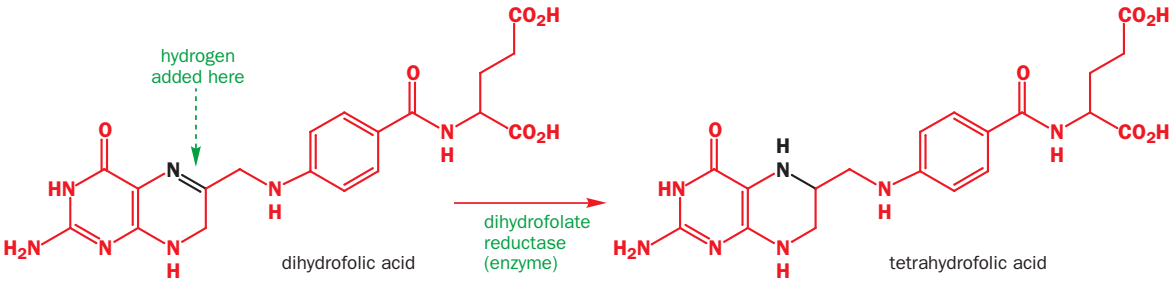


sulfamethoxypyridazine



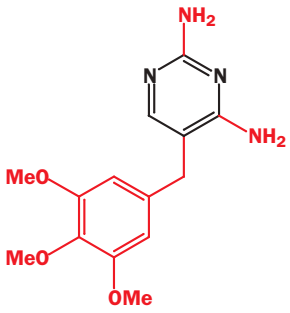
sulfamethoxazole

The next step in folic acid synthesis is the reduction of dihydrofolate to tetrahydrofolate. This can be done by both humans and bacteria and, although it looks like a rather trivial reaction (see black portion of molecules), it can only be done by the very important enzyme **dihydrofolate reductase**.



dihydrofolic acid

tetrahydrofolic acid



trimethoprim

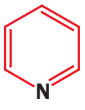
Though both bacteria and humans have this enzyme, the bacterial version is different enough for us to attack it with specific drugs. An example is trimethoprim—yet another heterocyclic compound with a pyrimidine core (black on diagram). These two types of drugs that attack the folic acid metabolism of bacteria are often used together.

We will see in the next chapter how to make these heterocyclic systems and, in Chapters 49–51, other examples of how important they are in living things.

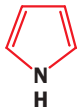
Which heterocyclic structures should you learn?

This is, of course, nearly a matter of personal choice. Every chemist really must know the names of the simplest heterocycles and we give those below along with a menu of suggestions.

First of all, those every chemist must know:



pyridine



pyrrole

thiophene

furan

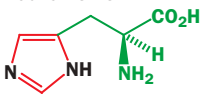
Now the table gives a suggested list of five ring systems that have important roles in the chemistry of life and in human medicine—many drugs are based on these five structures.

1 Imidazole

the most important five-membered ring with two nitrogen atoms

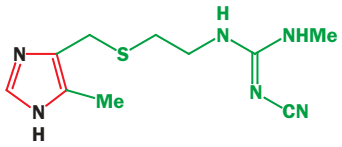
imidazole

part of the amino acid histidine, occurs in proteins and is important in enzyme mechanisms



the amino acid histidine

a substituted imidazole is an essential part of the anti-ulcer drug cimetidine



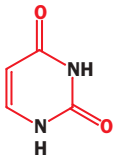
the anti-ulcer drug cimetidine (Tagamet)
a selective histidine mimic

2 Pyrimidine

the most important six-membered ring with two nitrogen atoms

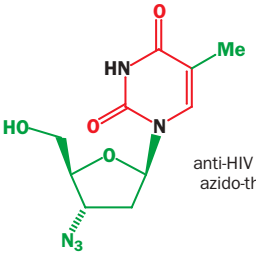
pyrimidine

three functionalized pyrimidines are part of DNA and RNA structure, e.g. uracil



uracil

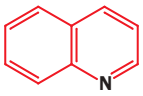
many antiviral drugs, particularly anti-HIV drugs, are modified pieces of DNA and contain pyrimidines



anti-HIV drug AZT azido-thymidine

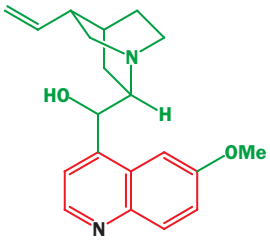
3 Quinoline

one of two benzo-pyridines with many applications



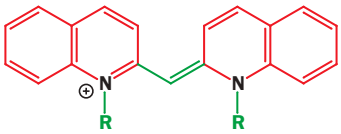
quinoline

occurs naturally in the important antimalarial drug quinine



quinine

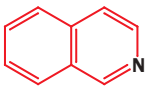
'cyanine' dyestuffs used as sensitizers for particular light wavelengths in colour photography



a "cyanine" dyestuff

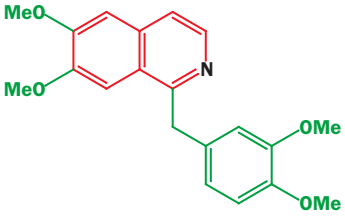
4 Isoquinoline

the other benzo-pyridine with many applications



isoquinoline

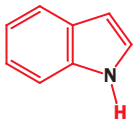
occurs naturally in the benzyl isoquinoline alkaloids like papaverine



papaverine—a benzyl isoquinoline alkaloid

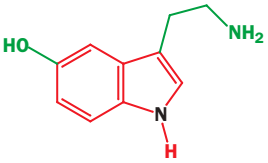
5 Indole

the more important benzo-pyrrole



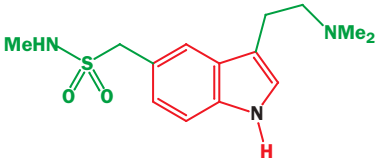
indole

occurs in proteins as tryptophan and in the brain as the neurotransmitter serotonin (5-hydroxy-tryptamine)



serotonin—a neurotransmitter

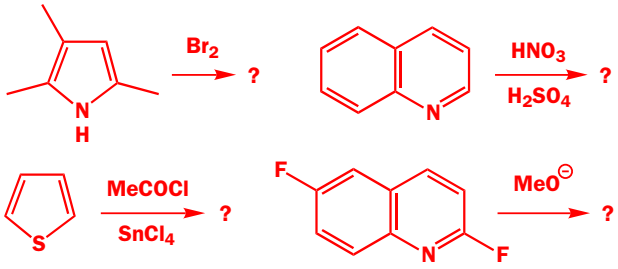
important modern drugs are based on serotonin including sumatriptan for migraine and ondansetron, an anti-emetic for cancer chemotherapy



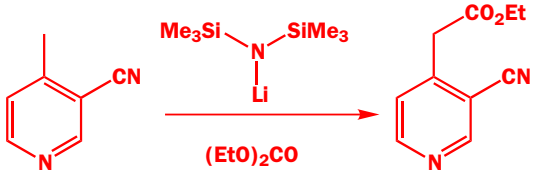
sumatriptan: for treatment of migraine

Problems

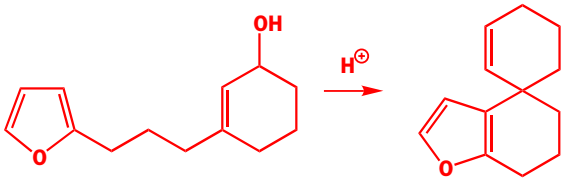
1. For each of the following reactions: (a) state what kind of substitution it suggests; (b) suggest what product might be formed if monosubstitution occurs.



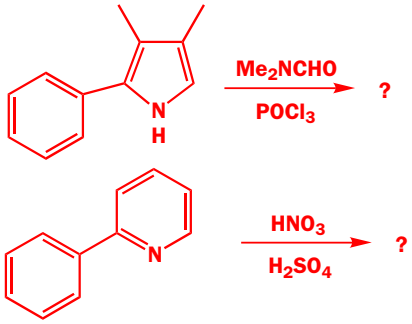
2. Give a mechanism for this side-chain extension of a pyridine.



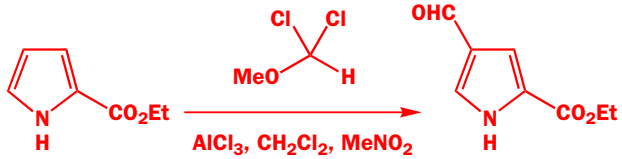
3. Give a mechanism for this reaction, commenting on the position on the furan ring that reacts.



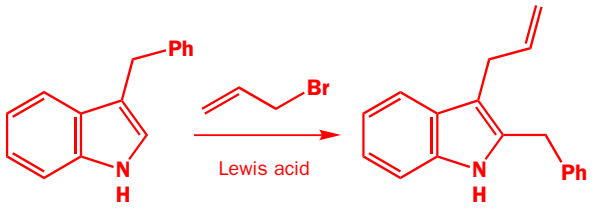
4. Suggest which product might be formed in each of these reactions and justify your choices.



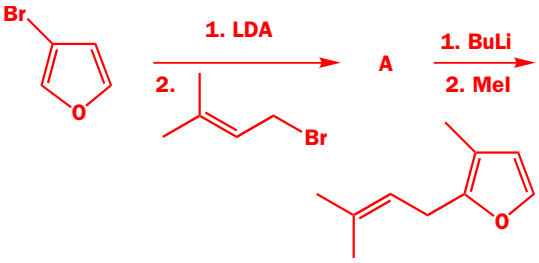
5. Comment on the mechanism and selectivity of this reaction of a pyrrole.



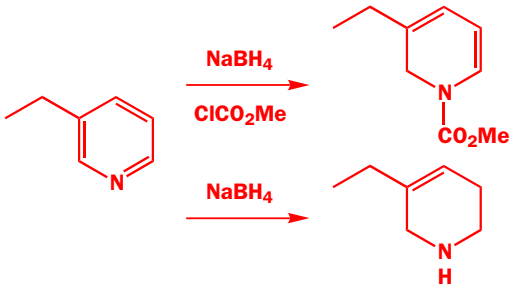
6. Explain the formation of the product in this Friedel–Crafts alkylation of an indole.



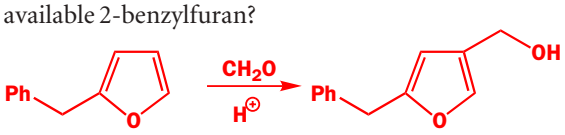
7. Explain the order of events and choice of bases in this sequence.



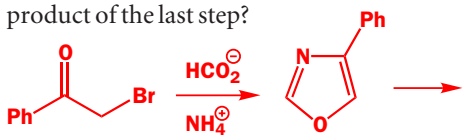
8. Explain the difference between these two pyridine reductions.

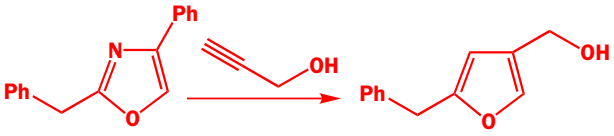


9. Why can this furan not be made by the direct route from available 2-benzylfuran?

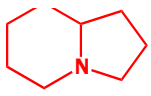


The same furan can be made by the route described below. Suggest mechanisms for the first and the last step. What is the other product of the last step?

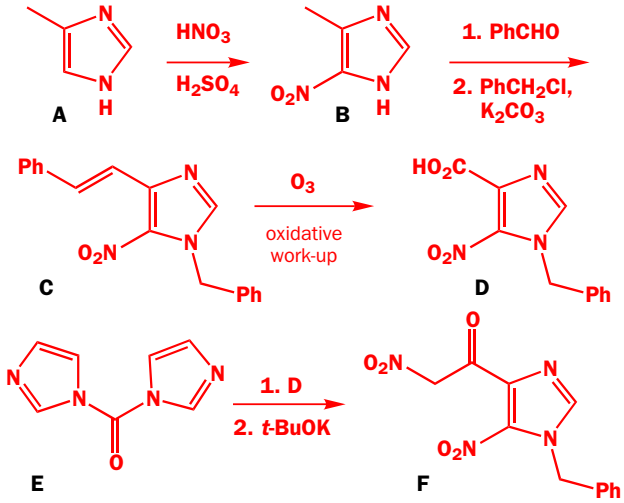




10. What aromatic system might be based on the skeleton given below? What sort of reactivity might it display?

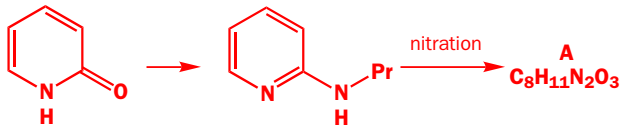


11. The reactions outlined in the chart below describe the early steps in a synthesis of an antiviral drug by the Parke–Davis company.



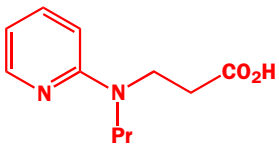
Consider how the reactivity of imidazoles is illustrated in these reactions, which involve not only the skeleton of the molecule but also the reagent E. You will need to draw mechanisms for the reactions and explain how they are influenced by the heterocycles.

12. Suggest how 2-pyridone might be converted into the amine shown. This amine undergoes mononitration to give compound A with the NMR spectrum given. What is the structure of A? Why is this isomer formed?

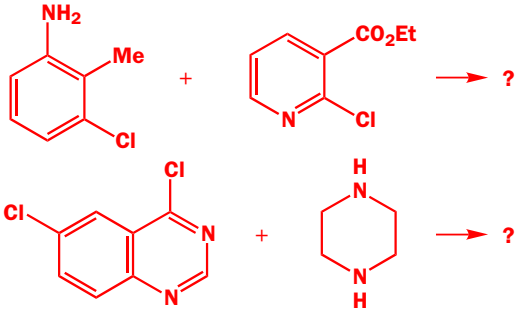


δ_H 1.0 p.p.m. (3H, t, *J* 7 Hz), 1.7 p.p.m. (2H, sextet, *J* 7 Hz), 3.3 p.p.m. (2H, q, *J* 7 Hz), 5.9 p.p.m. (1H, broad s), 6.4 p.p.m. (1H, d, *J* 8 Hz), 8.1 p.p.m. (1H, d, *J* 2 Hz), and 8.9 p.p.m. (1H, d, *J* 2 Hz).

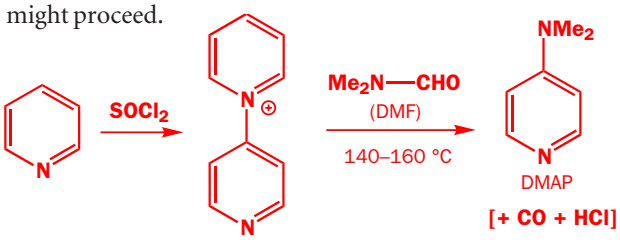
Compound A was needed for conversion into the potential enzyme inhibitor below. How might this be achieved?



13. Suggest what the products of these nucleophilic substitutions might be.



14. The synthesis of DMAP, the useful acylation catalyst mentioned in Chapters 8 and 12, is carried out by initial attack of thionyl chloride ($SOCl_2$) on pyridine. Suggest how the reactions might proceed.



Aromatic heterocycles 2: synthesis

44

Connections

Building on:

- Aromaticity ch7
- Enols and enolates ch21
- The aldol reaction ch27
- Acylation of enolates ch28
- Michael additions of enolates ch29
- Retrosynthetic analysis ch30
- Cycloadditions ch35
- Reactions of heterocycles ch43

Arriving at:

- Thermodynamics is on our side
- Disconnecting the carbon–heteroatom bonds first
- How to make pyrroles, thiophenes, and furans from 1,4-dicarbonyl compounds
- How to make pyridines and pyridones
- How to make pyridazines and pyrazoles
- How to make pyrimidines from 1,3-dicarbonyl compounds and amidines
- How to make thiazoles
- How to make isoxazoles and tetrazoles by 1,3-dipolar cycloadditions
- The Fischer indole synthesis
- Making drugs: Viagra, sumatriptan, ondansetron, indomethacin
- How to make quinolines and isoquinolines

Looking forward to:

- Biological chemistry ch49–ch51

In this chapter you will revisit the heterocyclic systems you have just met and find out how to make them. You'll also meet some new heterocyclic systems and find out how to make those. With so many heterocycles to consider, you'd be forgiven for feeling rather daunted by this prospect, but do not be alarmed. Making heterocycles is easy—that's precisely why there are so many of them. Just reflect . . .

- Making C–O, C–N, and C–S bonds is easy
- Intramolecular reactions are preferred to bimolecular reactions
- Forming five- and six-membered rings is easy
- We are talking about aromatic, that is, very stable molecules

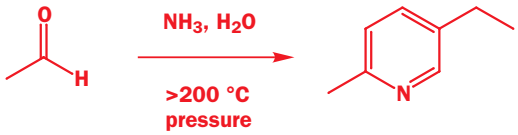
If we are to use those bullet points to our advantage we must think strategy before we start. When we were making benzene compounds we usually started with a preformed simple benzene derivative—toluene, phenol, aniline—and added side chains by electrophilic substitution. In this chapter our strategy will usually be to build the heterocyclic ring with most of its substituents already in place and add just a few others, perhaps by electrophilic substitution, but mostly by nucleophilic substitution.

We will usually make the rings by cyclization reactions with the heteroatom (O, N, S) as a nucleophile and a suitably functionalized carbon atom as the electrophile. This electrophile will almost always be a carbonyl compound of some sort and this chapter will help you revise your carbonyl chemistry from Chapters 6, 12, 14, 21, 23, and 26–29 as well as the approach to synthesis described in Chapter 30.

Thermodynamics is on our side

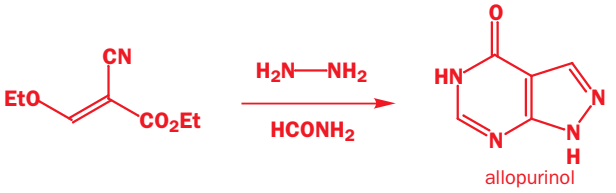
Some of the syntheses we will meet will be quite surprisingly simple! It sometimes seems that we can just mix a few things together with about the right number of atoms and let thermodynamics do the rest. A commercial synthesis of pyridines combines acetaldehyde and

ammonia under pressure to give a simple pyridine.



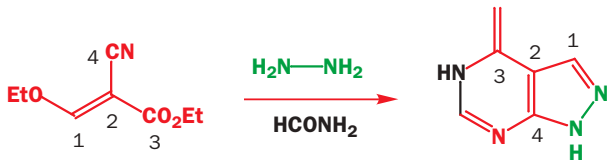
The yield is only about 50%, but what does that matter in such a simple process? By counting atoms we can guess that four molecules of aldehyde and one of ammonia react, but exactly how is a triumph of thermodynamics over mechanism. Much more complex molecules can sometimes be made very easily too. Take allopurinol, for example. One synthesis of this gout remedy goes like this.

■ Allopurinol was discussed in Chapter 43, p. 000.



allopurinol

It is not too difficult to work out where the atoms go—the hydrazine obviously gives rise to the pair of adjacent nitrogen atoms in the pyrazole ring and the ester group must be the origin of the carbonyl group (see colours and numbers on the right)—but would you have planned this synthesis?

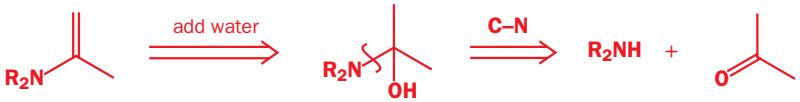


allopurinol

We will see that this sort of 'witch's brew' approach to synthesis is restricted to a few basic ring systems and that, in general, careful planning is just as important here as elsewhere. The difference here is that heterocyclic synthesis is very forgiving—it often 'goes right' instead of going wrong. We'll now look seriously at planning the synthesis of aromatic heterocycles.

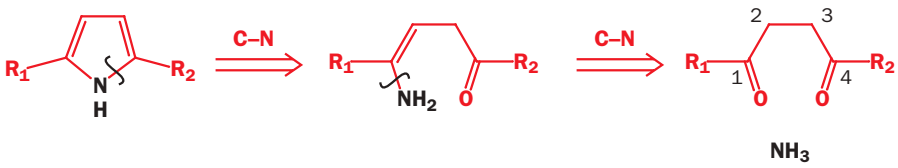
Disconnect the carbon–heteroatom bonds first

The simplest synthesis for a heterocycle emerges when we remove the heteroatom and see what electrophile we need. We shall use pyrroles as examples. The nitrogen forms an enamine on each side of the ring and we know that enamines are made from carbonyl compounds and amines.

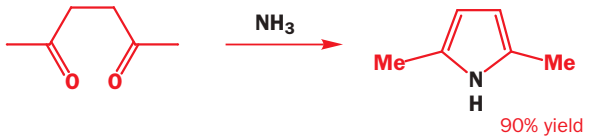


enamine amine ketone

If we do the same disconnection with a pyrrole, omitting the intermediate stage, we can repeat the C–N disconnection on the other side too:

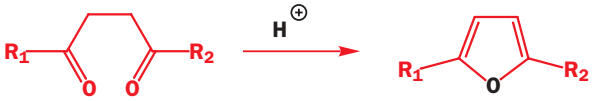


What we need is an amine—ammonia in this case—and a diketone. If the two carbonyl groups have a 1,4 relationship we will get a pyrrole out of this reaction. So hexane-2,5-dione reacts with ammonia to give a high yield of 2,5-dimethyl pyrrole.



90% yield

Making furans is even easier because the heteroatom (oxygen) is

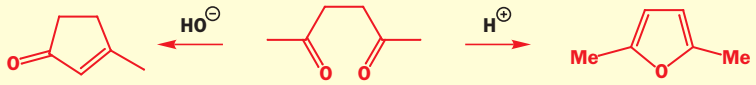


already there. All we have to do is to dehydrate the 1,4-diketone instead of making enamines from it. Heating with acid is enough.

Avoiding the aldol product

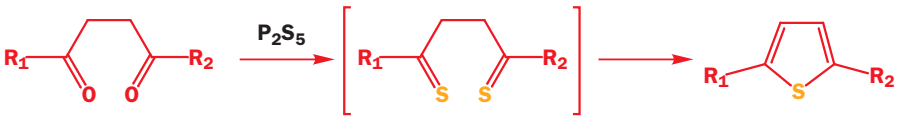
1,4-Diketones also self-condense rather easily in an intramolecular aldol reaction to give a cyclopentenone with an all-carbon five-membered ring. This too is a useful reaction but we need to know how to control it. The usual rule is:

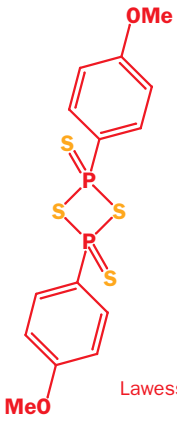
- Base gives the cyclopentenone
- Acid gives the furan



cyclopentenone 1,4-diketone furan

For thiophenes we could in theory use H_2S or some other sulfur nucleophile but, in practice, an electrophilic reagent is usually used to convert the two C=O bonds to C=S bonds. Thioketones are much less stable than ketones and cyclization is swift. Reagents such as P_2S_5 or Lawesson's reagent are the usual choice here.





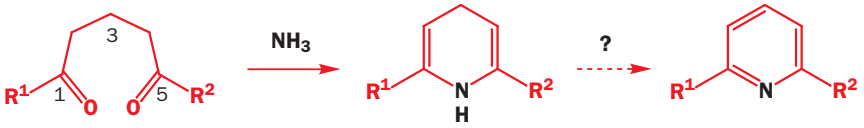
Lawesson's reagent

▶ Sulfur chemistry is discussed in Chapter 46; all we will say here about the mechanisms of these reactions is that phosphorus is commonly used to remove oxygen and replace it by another element: remember the Mitsunobu reaction?

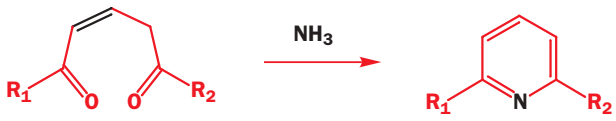
Making five-membered heterocycles

Cyclization of 1,4-dicarbonyl compounds with nitrogen, sulfur, or oxygen nucleophiles gives the five-membered aromatic heterocycles pyrrole, thiophene, and furan.

It seems a logical extension to use a 1,5-diketone to make substituted pyridines but there is a slight problem here as we will introduce only two of the required three double bonds when the two enamines are formed.



To get the pyridine by enamine formation we should need a double bond somewhere in the chain between the two carbonyl groups. But here another difficulty arises—it will have to be a *cis* (*Z*) double bond or cyclization would be impossible.



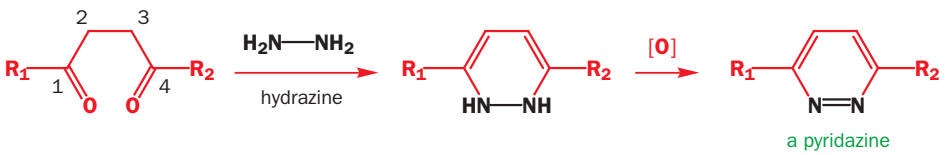
On the whole it is easier to use the saturated 1,5-diketone and oxidize the product to the pyridine. As we are going from a nonaromatic to an aromatic compound, oxidation is easy and we can replace the question mark above with almost any simple oxidizing agent, as we shall soon see.

Making six-membered heterocycles

Cyclization of 1,5-dicarbonyl compounds with nitrogen nucleophiles leads to the six-membered aromatic heterocycle pyridine.

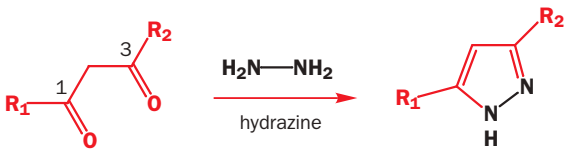
Heterocycles with two nitrogen atoms come from the same strategy

Reacting a 1,4-diketone with hydrazine (NH_2NH_2) makes a double enamine again and this is only an oxidation step away from a pyridazine. This is again a good synthesis.



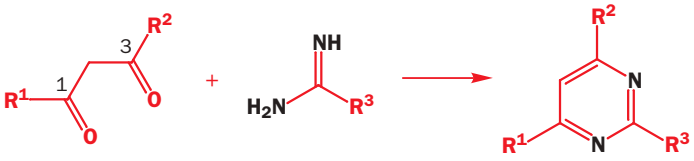
a pyridazine

If we use a 1,3-diketone instead we will get a five-membered heterocycle and the imine and enamine formed are enough to give aromaticity without any need for oxidation. The product is a pyrazole.



a pyrazole

The two heteroatoms do not, of course, need to be joined together for this strategy to work. If an amidine is combined with the same 1,3-diketone we get a six-membered heterocycle. As the nucleophile contains one double bond already, an aromatic pyrimidine is formed directly.

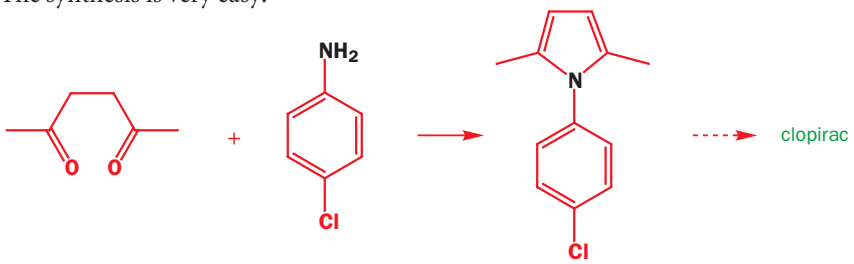


an amidine a pyrimidine

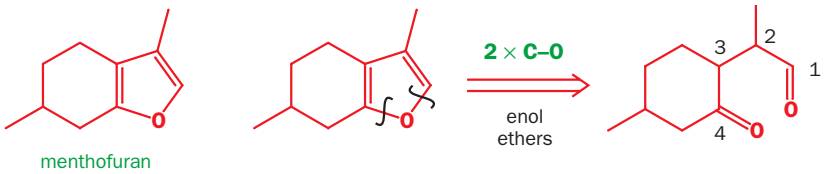
Since diketones and other dicarbonyl compounds are easily made by enolate chemistry (Chapters 26–30) this strategy has been very popular and we will look at some detailed examples before moving on to more specialized reactions for the different classes of aromatic heterocycles.

Pyrroles, thiophenes, and furans from 1,4-dicarbonyl compounds

We need to make the point that pyrrole synthesis can be done with primary amines as well as with ammonia and a good example is the pyrrole needed for clopirac, a drug we discussed in Chapter 43. The synthesis is very easy.



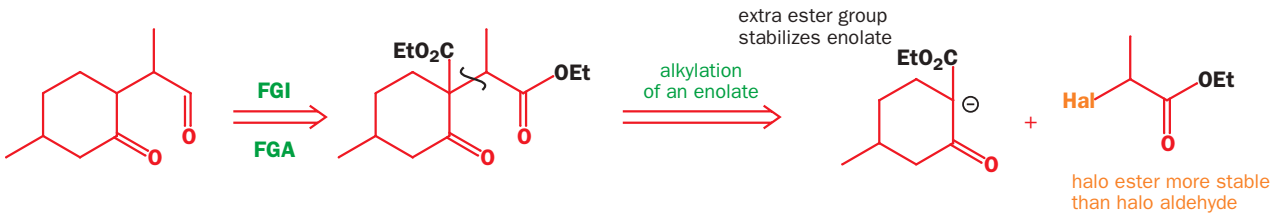
For an example of furan synthesis we choose menthofuran, which contributes to the flavour of mint. It has a second ring, but that is no problem if we simply disconnect the enol ethers as we have been doing so far.



menthofuran

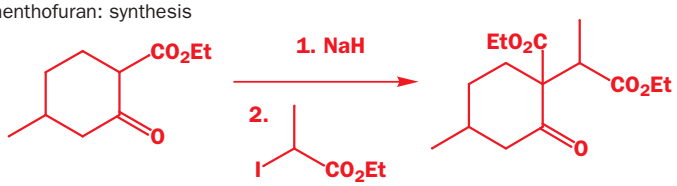
The starting material is again a 1,4-dicarbonyl compound but as there was no substituent at C1 of the furan, that atom is an aldehyde rather than a ketone. This might lead to problems in the synthesis so a few changes (using the notation you met in Chapter 30) are made to the intermediate before further disconnection.

▶ α-Halo aldehydes are unstable and should be avoided.

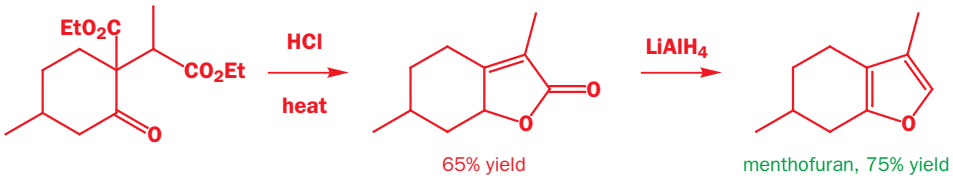


Notice in particular that we have 'oxidized' the aldehyde to an ester to make it more stable—in the synthesis reduction will be needed. Here is the alkylation step of the synthesis, which does indeed go very well with the α-iodo-ester.

menthofuran: synthesis



Cyclization with acid now causes a lot to happen. The 1,4-dicarbonyl compound cyclizes to a lactone, not to a furan, and the redundant ester group is lost by hydrolysis and decarboxylation. Notice that the double bond moves into conjugation with the lactone carbonyl group. Finally, the reduction gives the furan. No special precautions are necessary—as soon as the ester is partly reduced, it loses water to give the furan whose aromaticity prevents further reduction even with $LiAlH_4$.

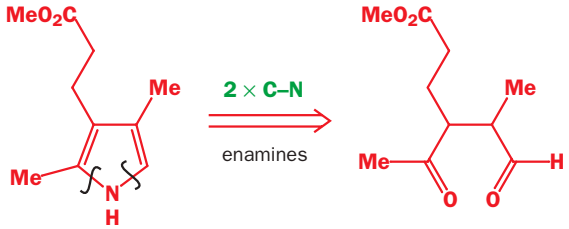


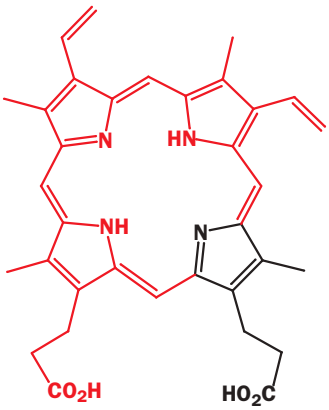
A reminder

Cyclization of 1,4-dicarbonyl compounds with nitrogen, sulfur, or oxygen nucleophiles gives the five-membered aromatic heterocycles pyrrole, thiophene, and furan.

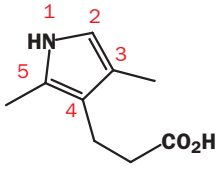
Now we need to take these ideas further and discuss an important pyrrole synthesis that follows this strategy but includes a cunning twist. It all starts with the porphyrin found in blood. In Chapter 43 we gave the structure of that very important compound and showed that it contains four pyrrole rings joined in a macrocycle. We are going to look at one of those pyrroles.

Porphyrins can be made by joining together the various pyrroles in the right order and what is needed for this one (and also, in fact, for another—the one in the north-east corner of the porphyrin) is a pyrrole with the correct substituents in positions 3 and 4, a methyl group in position 5, and a hydrogen atom at position 2. Position 2 must be free. Here is the molecule drawn somewhat more conveniently together with the disconnection we have been using so far.





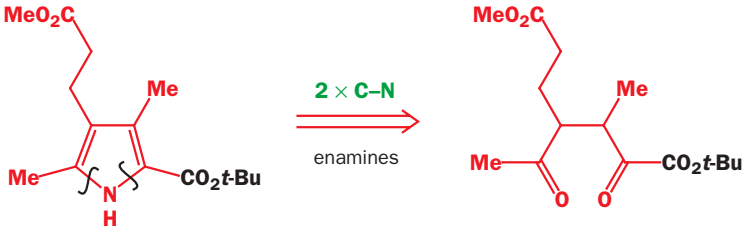
the porphyrin in haemoglobin



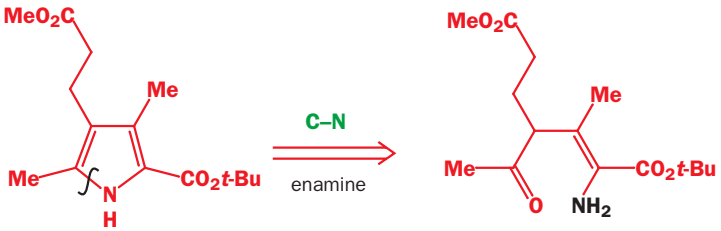
component pyrrole

See p. 000 for a discussion of pyrrole reactivity.

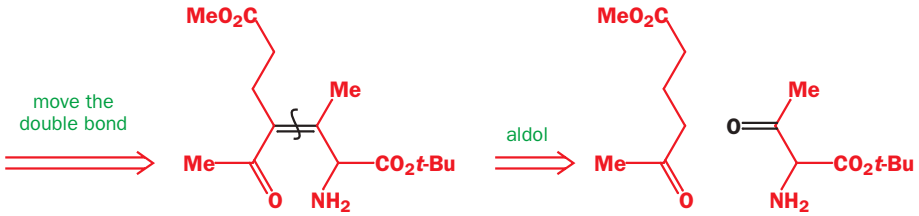
No doubt such a synthesis could be carried out but it is worth looking for alternatives for a number of reasons. We would prefer not to make a pyrrole with a free position at C2 as that would be very reactive and we know from Chapter 43 that we can block such a position with a *t*-butyl ester group. This gives us a very difficult starting material with four different carbonyl groups.



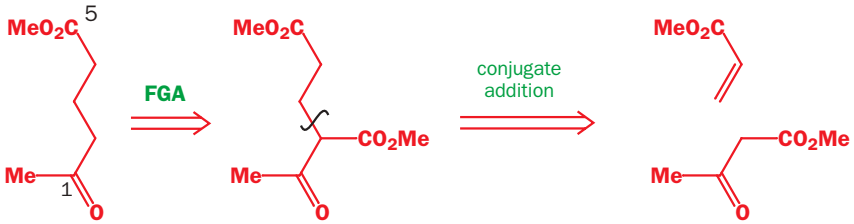
We have made a problem for ourselves by having two carbonyl groups next to each other. Could we escape from that by replacing one of them with an amine? We should then have an ester of an α amino acid, an attractive starting material, and this corresponds to disconnecting just one of the C–N bonds.



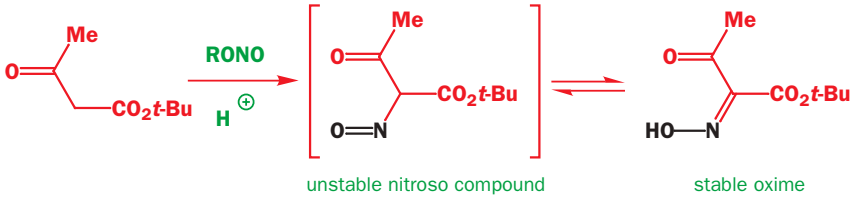
At first we seem to have made no progress but just see what happens when we move the double bond round the ring into conjugation with the ketone. After all, it doesn't matter where the double bond starts out—we will always get the aromatic product.



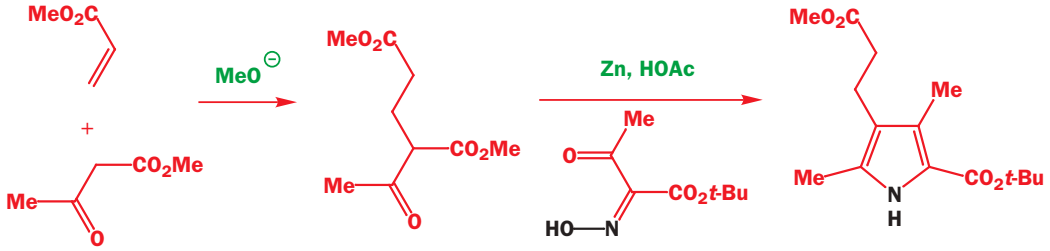
Each of our two much simpler starting materials needs to be made. The keto-ester is a 1,5-dicarbonyl compound so it can be made by a conjugate addition of an enolate, a process greatly assisted by the addition of a second ester group (Chapter 29).



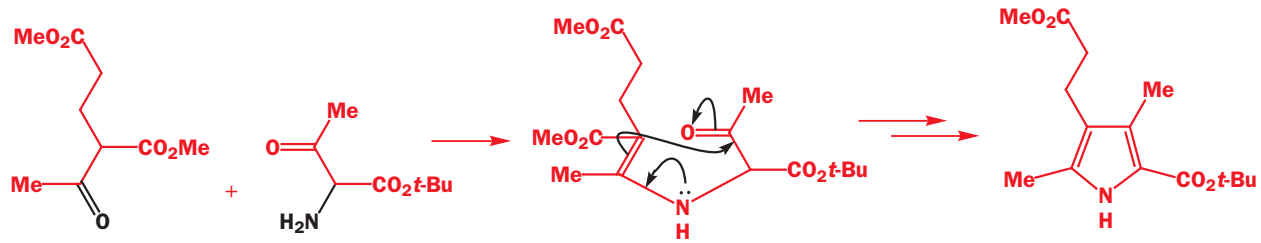
The other compound is an amino-keto-ester and will certainly react with itself if we try to prepare it as a pure compound. The answer is to release it into the reaction mixture and this can be done by nitrosation and reduction (Chapter 21) of another stable enolate.



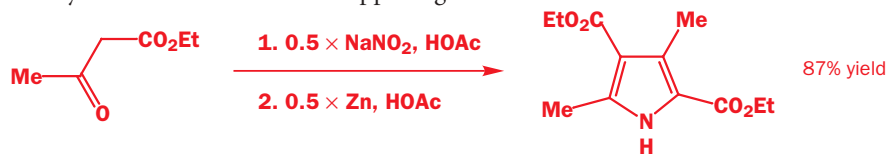
Zinc in acetic acid (Chapter 24) reduces the oxime to the amine and we can start the synthesis by doing the conjugate addition and then reducing the oxime in the presence of the keto-diester.



This reaction forms the required pyrrole in one step! First, the oxime is reduced to an amine; then the amino group forms an imine with the most reactive carbonyl group (the ketone) in the keto-diester. Finally, the very easily formed enamine cyclizes on to the other ketone.

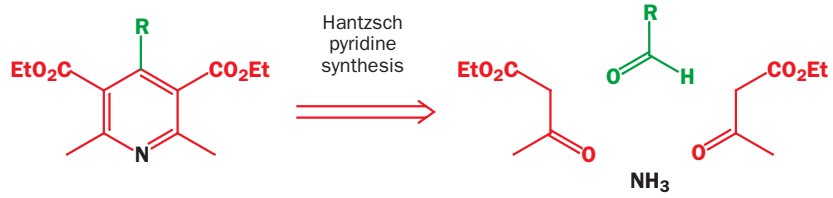


This pyrrole synthesis is important enough to be given the name of its inventor—it is the **Knorr pyrrole synthesis**. Knorr himself made a rather simpler pyrrole in a remarkably efficient reaction. See if you can work out what is happening here.

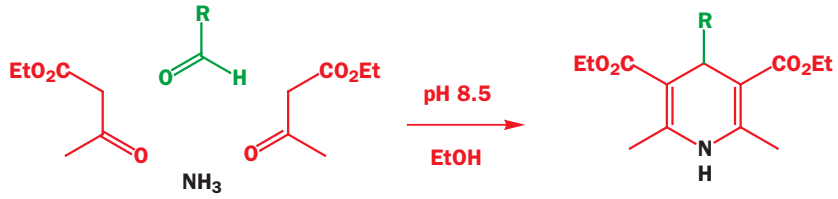


How to make pyridines: the Hantzsch pyridine synthesis

The idea of coupling two keto-esters together with a nitrogen atom also works for pyridines except that an extra carbon atom is needed. This is provided as an aldehyde and another important difference is that the nitrogen atom is added as a nucleophile rather than an electrophile. These are features of the **Hantzsch pyridine synthesis**. This is a four-component reaction that goes like this.



You are hardly likely to understand the rationale behind this reaction from that diagram so let's explore the details. The product of the reaction is actually the dihydropyridine, which has to be oxidized to the pyridine by a reagent such as HNO_3, Ce(IV), or a quinone.



the dihydropyridine

▶ Standard heterocyclic syntheses tend to have a name associated with them and it is simply not worth while learning these names. Few chemists use any but the most famous of them: we will mention the Knorr pyrrole synthesis, the Hantzsch pyridine synthesis, and the Fischer and Reissert indole syntheses. We did not mention that the synthesis of furans from 1,4-dicarbonyl compounds is known as the Feist–Benary synthesis, and there are many more like this. If you are really interested in these other names we suggest you consult a specialist book on heterocyclic chemistry.

■ Arthur Hantzsch, 1857–1935, the 'fiery stereochemist' of Leipzig, is most famous for the work he did with Werner at the ETH in Zurich where in 1890 he suggested that oximes could exist in *cis* and *trans* forms.

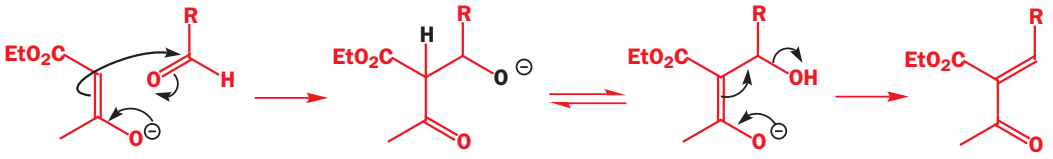
The reaction is very simply carried out by mixing the components in the right proportions in ethanol. The presence of water does not spoil the reaction and the ammonia, or some added amine, ensures the slightly alkaline pH necessary. Any aldehyde can be used, even formaldehyde, and yields of the crystalline dihydropyridine are usually very good.

This reaction is an impressive piece of molecular recognition by small molecules and writing a detailed mechanism is a bold venture. We can see that certain events have to happen. The ammonia has to attack the ketone groups, but it would prefer to attack the more electrophilic aldehyde so this is probably not the first step. The enol or enolate of the keto-ester has to attack the aldehyde (twice!) so let us start there.

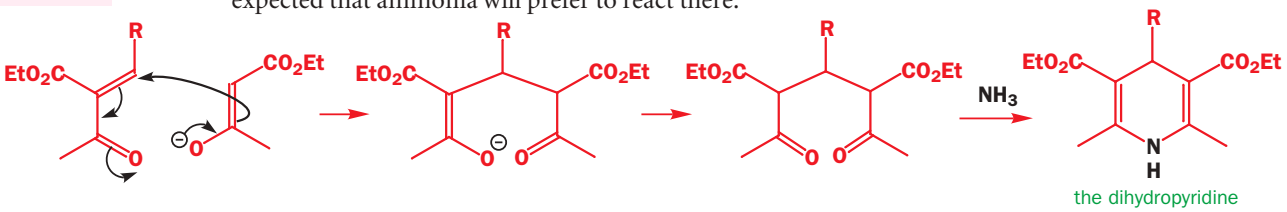
▶The mechanism of the Hantzsch pyridine synthesis

Several of these steps could be done in different orders but the essentials are:

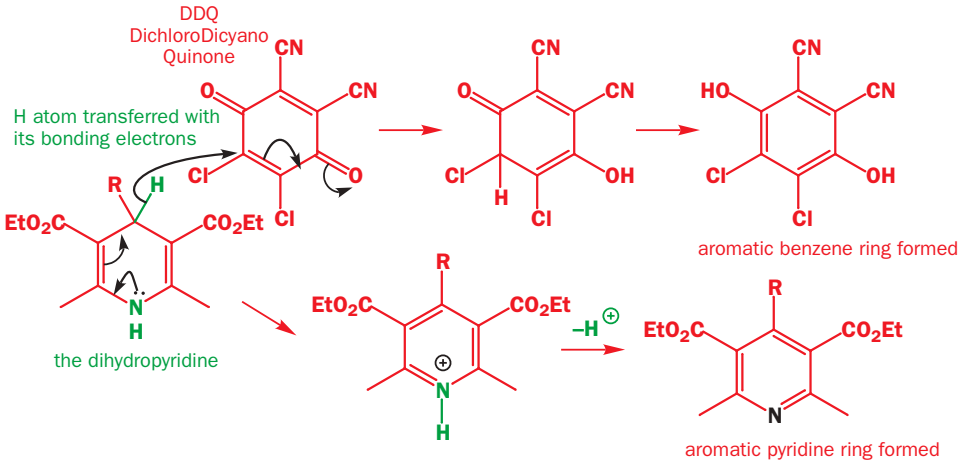
- aldol reaction between the aldehyde and the keto-ester
- Michael (conjugate) addition to the enone
- addition of ammonia to one ketone
- cyclization of the imine or enamine on to the other ketone



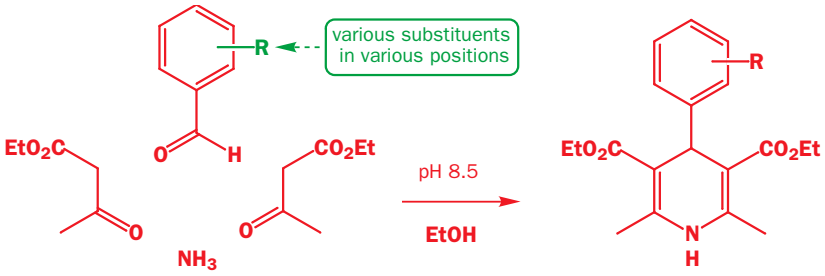
This adduct is in equilibrium with the stable enolate from the keto-ester and elimination now gives an unsaturated carbonyl compound. Such chemistry is associated with the aldol reactions we discussed in Chapter 27. The new enone has two carbonyl groups at one end of the double bond and is therefore a very good Michael acceptor (Chapter 29). A second molecule of enolate does a conjugate addition to complete the carbon skeleton of the molecule. Now the ammonia attacks either of the ketones and cyclizes on to the other. As ketones are more electrophilic than esters it is to be expected that ammonia will prefer to react there.



The necessary oxidation is easy both because the product is aromatic and because the nitrogen atom can help to expel the hydrogen atom and its pair of electrons from the 4-position. If we use a quinone as oxidizing agent, both compounds become aromatic in the same step. We will show in Chapter 50 that Nature uses related dihydropyridines as reducing agents in living things.

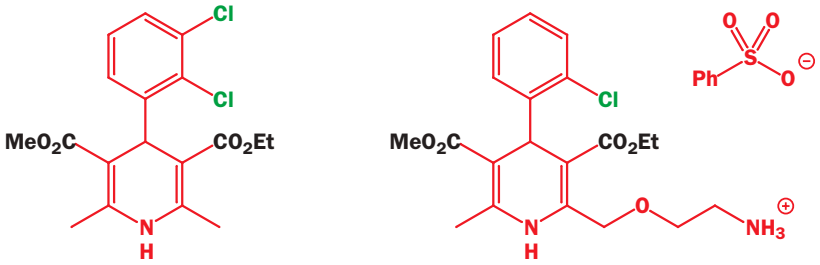


The Hantzsch pyridine synthesis is an old discovery (1882) which sprang into prominence in the 1980s with the discovery that the dihydropyridine intermediates prepared from aromatic aldehydes are calcium channel blocking agents and therefore valuable drugs for heart disease with useful effects on angina and hypertension.



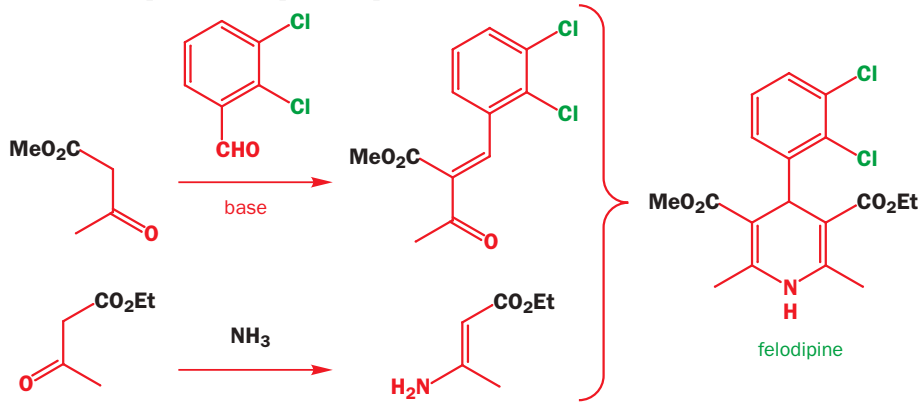
These drugs inhibit Ca^{2+} ion transport across cell membranes and relax muscle tissues selectively without affecting the working of the heart. Hence high blood pressure can be reduced. Pfizer's amlodipine (Istin™ or Norvasc™) is a very important drug—it had sales of 1.6 billion dollars in 1996.

So far, so good. But it also became clear that the best drugs were unsymmetrical—some in a trivial way such as felodipine but some more seriously such as Pfizer's amlodipine. At first sight it looks as though the very simple and convenient Hantzsch synthesis cannot be used for these compounds.



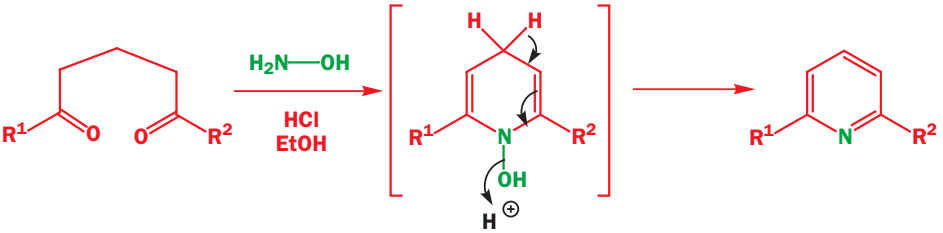
felodipine amlodipine

Clearly, a modification is needed in which half of the molecule is assembled first. The solution lies in early work by Robinson who made the very first enamines from keto-esters and amines. One half of the molecule is made from an enamine and the other half from a separately synthesized enone. We can use felodipine as a simple example.

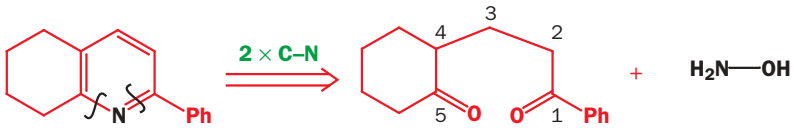


Other syntheses of pyridines

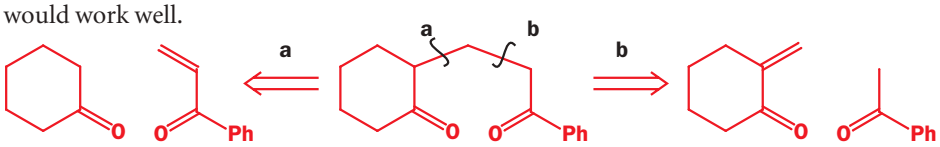
The Hantzsch synthesis produces a reduced pyridine but there are many syntheses that go directly to pyridines. One of the simplest is to use hydroxylamine (NH_2OH) instead of ammonia as the nucleophile. Reaction with a 1,5-diketone gives a dihydropyridine but then water is lost and no oxidation is needed.



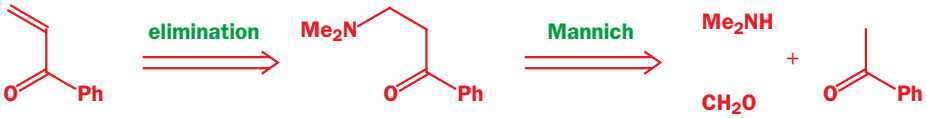
The example below shows how these 1,5-diketones may be quickly made by the Mannich (Chapter 27) and Michael (Chapter 29) reactions. Our pyridine has a phenyl substituent and a fused saturated ring. First we must disconnect to the 1,5-diketone.



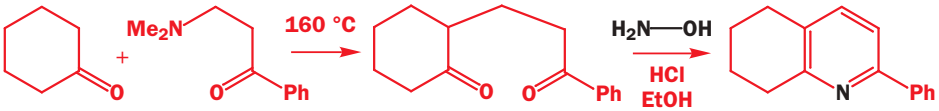
Further disconnection reveals a ketone and an enone. There is a choice here and both alternatives would work well.

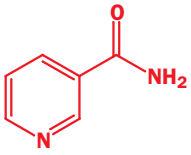


It is convenient to use Mannich bases instead of the very reactive unsaturated ketones and we will continue with disconnection 'a'.

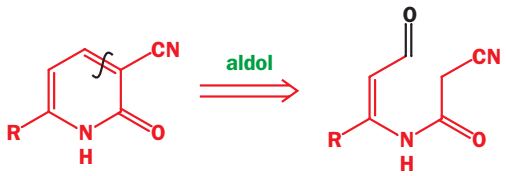


The synthesis is extraordinarily easy. The stable Mannich base is simply heated with the other ketone to give a high yield of the 1,5-diketone. Treatment of that with the HCl salt of NH_2OH in EtOH gives the pyridine directly, also in good yield.

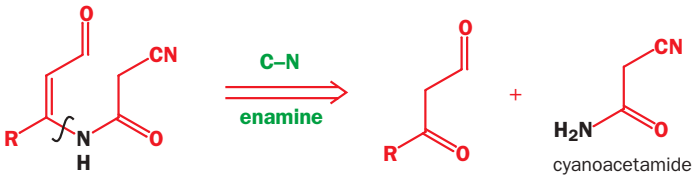



nicotinamide

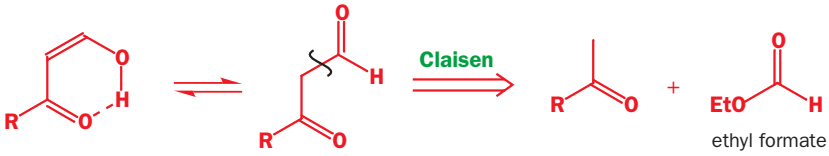
Another direct route leads, as we shall now demonstrate, to pyridones. These useful compounds are the basis for nucleophilic substitutions on the ring (Chapter 43). We choose an example that puts a nitrile in the 3-position. This is significant because the role of nicotinamide in living things (Chapter 50) makes such products interesting to make. Aldol disconnection of a 3-cyano pyridone starts us on the right path.



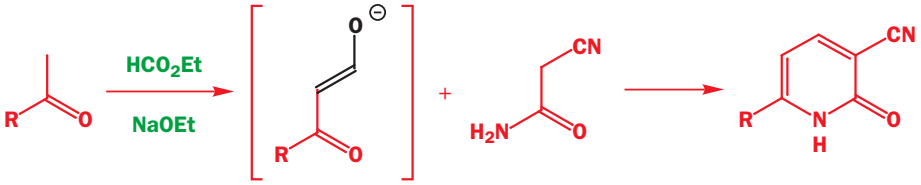
If we now disconnect the C–N bond forming the enamine on the other side of the ring we will expose the true starting materials. This approach is unusual in that the nitrogen atom that is to be the pyridine nitrogen is not added as ammonia but is already present in a molecule of cyanoacetamide.



The keto-aldehyde can be made by a simple Claisen ester condensation (Chapter 28) using the enolate of the methyl ketone with ethyl formate (HCO_2Et) as the electrophile. It actually exists as a stable enol, like so many 1,3-dicarbonyl compounds (Chapter 21).

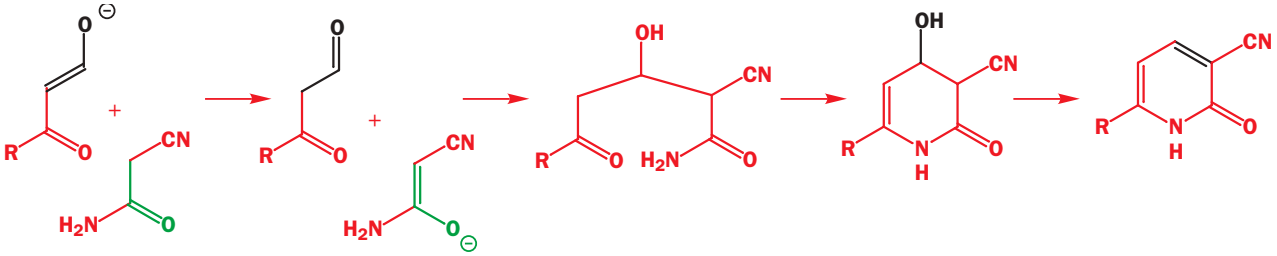


In the synthesis, the product of the Claisen ester condensation is actually the enolate anion of the keto-aldehyde and this can be combined directly without isolation with cyanoacetamide to give the pyridone in the same flask.



What must happen here is that the two compounds must exchange protons (or switch enolates if you prefer) before the aldol reaction occurs. Cyclization probably occurs next through C–N bond formation and, finally, dehydration is forced to give the *Z*-alkene.

▶ If dehydration occurred first, only the *Z*-alkene could cyclize and the major product, the *E*-alkene, would be wasted.



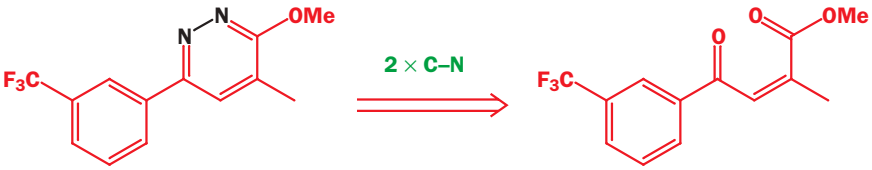
In planning the synthesis of a pyrrole or a pyridine from a dicarbonyl compound, considerable variation in oxidation state is possible. The oxidation state is chosen to make further disconnection of the carbon skeleton as easy as possible. We can now see how these same principles can be applied to pyrazoles and pyridazines.

Pyrazoles and pyridazines from hydrazine and dicarbonyl compounds

Disconnection of pyridazines reveals a molecule of hydrazine and a 1,4-diketone with the proviso that, just as with pyridines, the product will be a dihydropyrazine and oxidation will be needed to give the aromatic compound. As with pyridines, we prefer to avoid the *cis* double bond problem.

As an example we can take the cotton herbicide made by Cyanamid. Direct removal of hydrazine would require a *cis* double bond in the starting material.

▶ The herbicide kills weeds in cotton crops rather than the cotton plant itself!

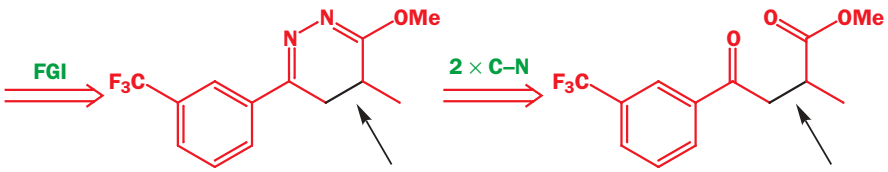


Cyanamid cotton herbicide

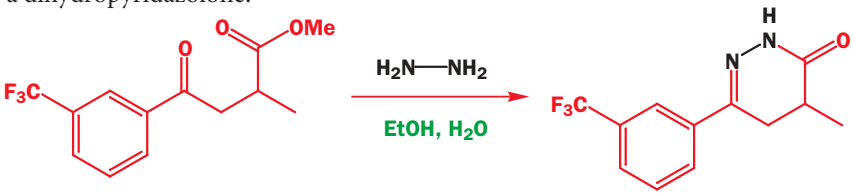
reject *cis* alkene as starting material

If we remove the double bond first, a much simpler compound emerges. Note that this is a keto-ester rather than a diketone.

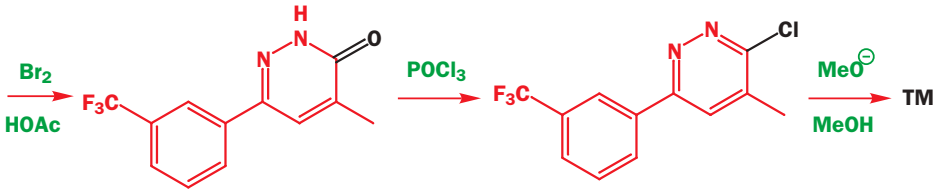
▶ The alkylation is regioselective because the methylated nitrogen must become the pyrrole-like nitrogen atom and the molecule prefers the longest conjugated system involving that nitrogen and the ester.



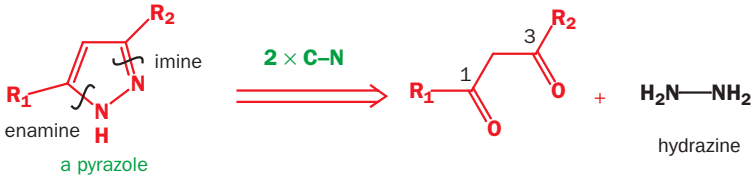
When hydrazine is added to the keto-ester an imine is formed with the ketone but acylation occurs at the ester end to give an amide rather than the imino-ester we had designed. The product is a dihydropyridazolone.



Aromatization with bromine gives the aromatic pyridazolone by bromination and dehydrobromination and now we invoke the nucleophilic substitution reactions introduced in Chapter 43. First we make the chloride with $POCl_3$ and then displace with methanol.

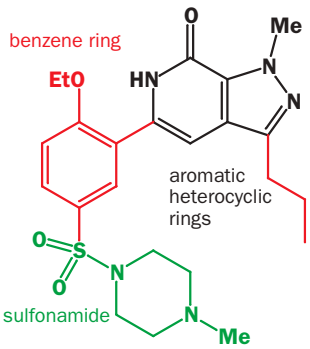


The five-membered ring pyrazoles are even simpler as the starting material is a 1,3-dicarbonyl compound available from the aldol or Claisen ester condensations.



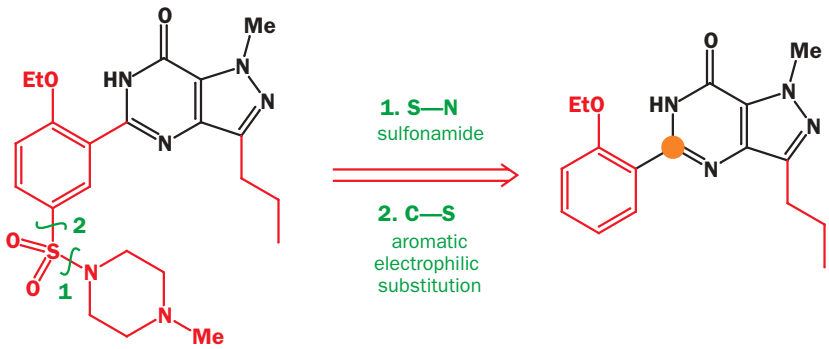
Chemistry hits the headlines—Viagra

Viagra:
Pfizer's treatment for male erectile dysfunction

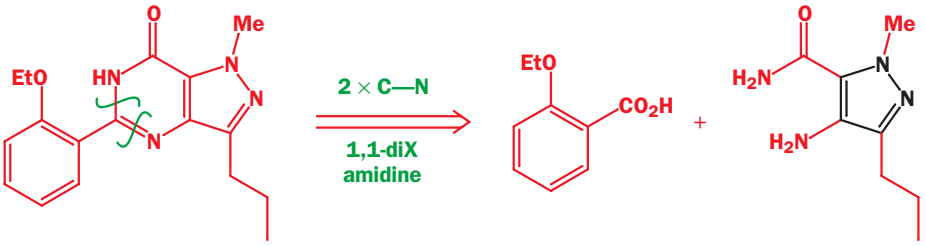


In 1998 chemistry suddenly appeared in the media in an exceptional way. Normally not a favourite of TV or the newspapers, chemistry produced a story with all the right ingredients—sex, romance, human ingenuity—and all because of a pyrazole. In the search for a heart drug, Pfizer uncovered a compound that allowed impotent men to have active sex lives. They called it Viagra.

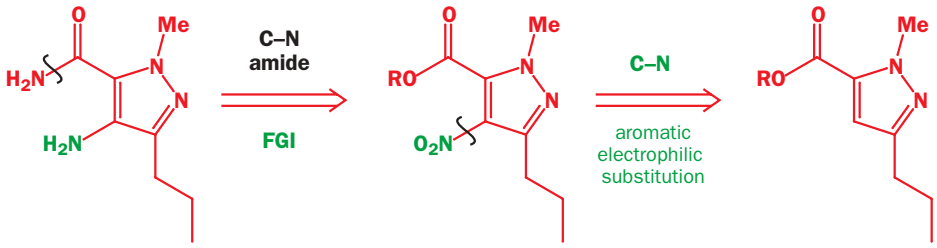
The molecule contains a sulfonamide and a benzene ring as well as the part that interests us most—a bicyclic aromatic heterocyclic system of a pyrazole fused to a pyrimidine. We shall discuss in detail how Pfizer made this part of the molecule and just sketch in the rest. The sulfonamide can be made from the sulfonic acid that can be added to the benzene ring by electrophilic aromatic sulfonation (Chapter 22).



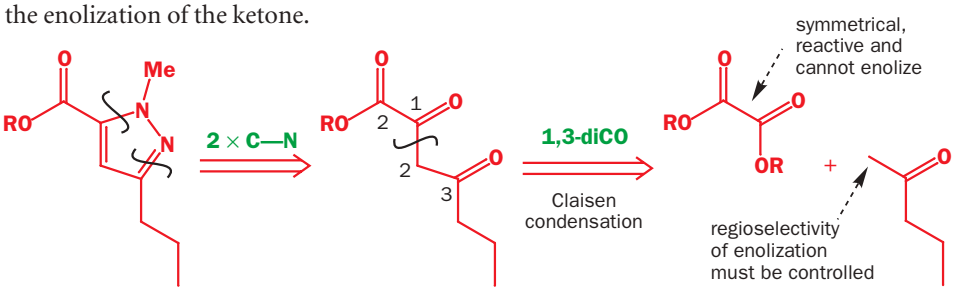
Inspection of what remains reveals that the carbon atom atom in the heterocycles next to the benzene ring (marked with an orange blob) is at the oxidation level of a carboxylic acid. If, therefore, we disconnect both C–N bonds to this atom we will have two much simpler starting materials.



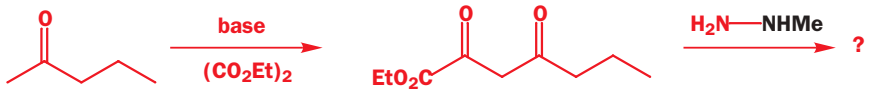
The aromatic acid is available and we need consider only the pyrazole (core pyrazole ring in black in the diagram). The aromatic amino group can be put in by nitration and reduction and the amide can be made from the corresponding ester. This leaves a carbon skeleton, which must be made by ring synthesis.



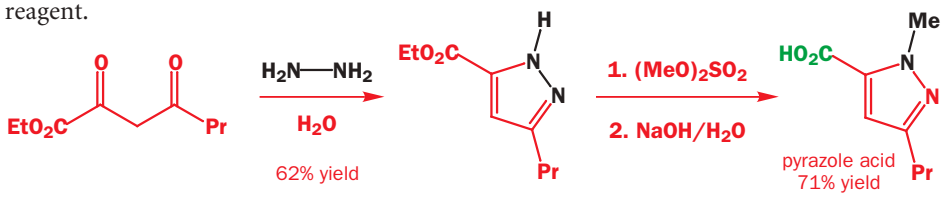
Following the methods we have established so far in this chapter, we can remove the hydrazine portion to reveal a 1,3-dicarbonyl compound. In fact, this is a tricarbonyl compound, a diketo-ester, because of the ester already present and it contains 1,2- 1,3-, and 1,4-dicarbonyl relationships. The simplest synthesis is by a Claisen ester condensation and we choose the disconnection so that the electrophile is a reactive (oxalate) diester that cannot enolize. The only control needed will then be in the enolization of the ketone.



The Claisen ester condensation gives the right product just by treatment with base. The reasons for this are discussed in Chapter 28. We had then planned to react the keto-diester with methylhydrazine but there is a doubt about the regioselectivity of this reaction—the ketones are more electrophilic than the ester all right, but which ketone will be attacked by which nitrogen atom?

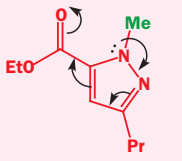


We have already seen the solution to this problem in Chapter 43. If we use symmetrical hydrazine, we can deal with the selectivity problem by alkylation. Dimethyl sulfate turns out to be the best reagent.

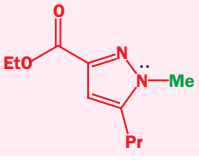


▶ The alkylation is regioselective because the methylated nitrogen must become the pyrrole-like nitrogen atom and the molecule prefers the longest conjugated system involving that nitrogen and the ester.

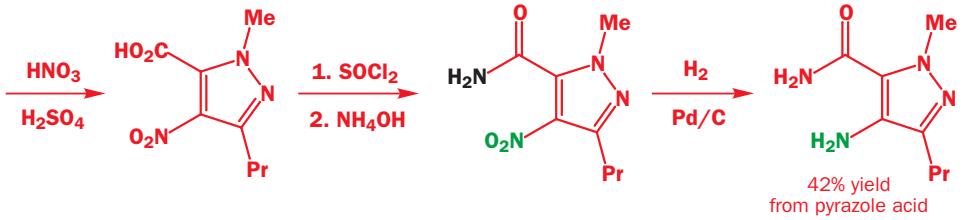
lone pair delocalized into ester carbonyl group



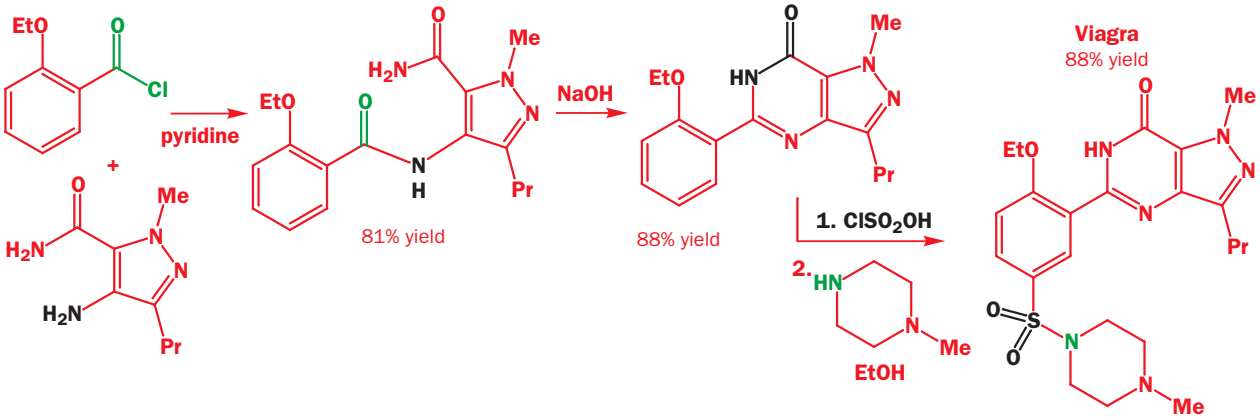
lone pair not delocalized into ester carbonyl group



The stable pyrazole acid from the hydrolysis of this ester is a key intermediate in Viagra production. Nitration can occur only at the one remaining free position and then amide formation and reduction complete the synthesis of the amino pyrazole amide ready for assembly into Viagra.

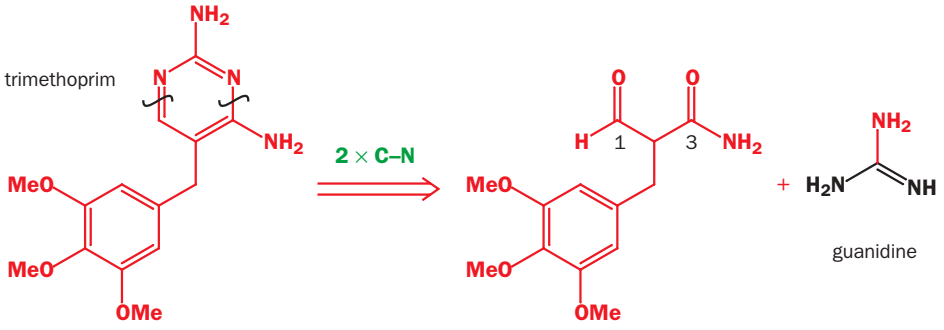


The rest of the synthesis can be summarized very briefly as it mostly concerns material outside the scope of this chapter. You might like to notice how easy the construction of the second heterocyclic ring is—the nucleophilic attack of the nitrogen atom of one amide on to the carbonyl of another would surely not occur unless the product were an aromatic heterocycle.

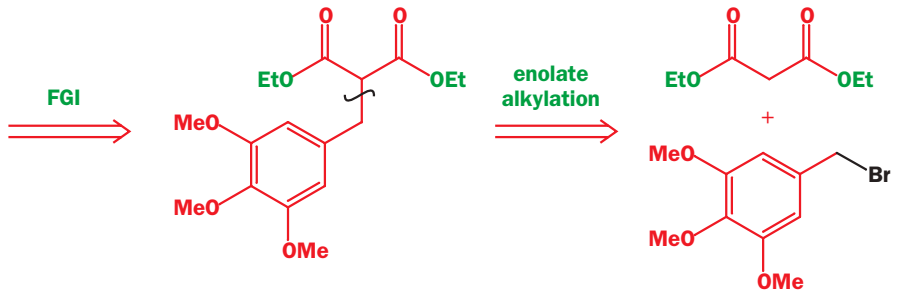


Pyrimidines can be made from 1,3-dicarbonyl compounds and amidines

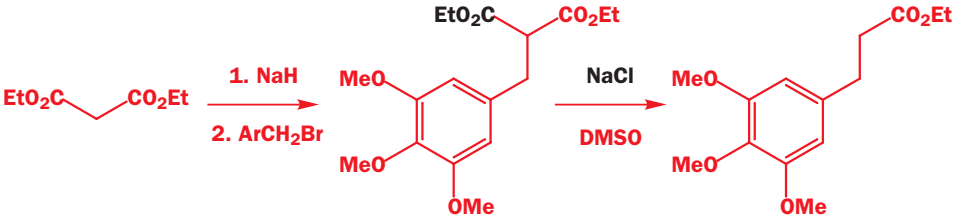
In Chapter 43 we met some compounds that interfere in folic acid metabolism and are used as antibacterial agents. One of them was trimethoprim and it contains a pyrimidine ring (black on the diagram). We are going to look at its synthesis briefly because the strategy used is the opposite of that used with the pyrimidine ring in Viagra. Here we disconnect a molecule of guanidine from a 1,3-dicarbonyl compound.



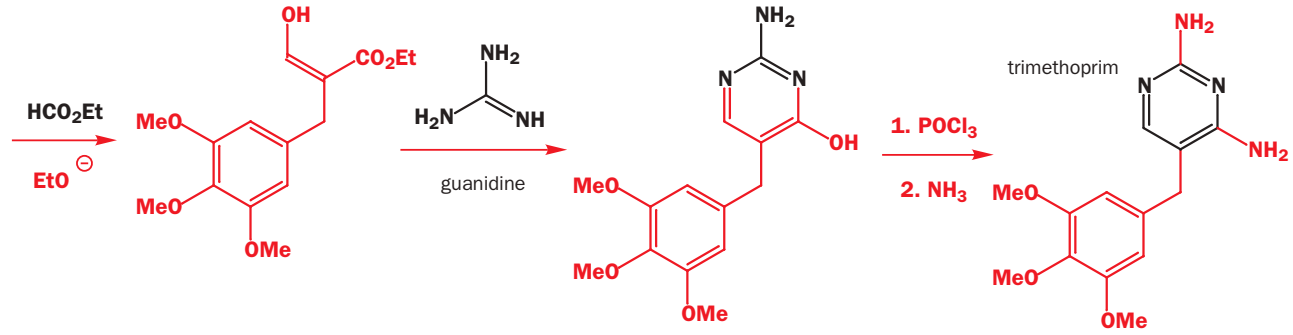
The 1,3-dicarbonyl compound is a combination of an aldehyde and an amide but is very similar to a malonic ester so we might think of making this compound by alkylation of that stable enolate (Chapter 26) with the convenient benzylic bromide.



The alkylation works fine but it turns out to be better to add the aldehyde as an electrophile (cf. the pyridone synthesis on p. 000) rather than try to reduce an ester to an aldehyde. The other ester is already at the right oxidation level. Notice the use of the NaCl method of decarboxylation (Chapter 26).

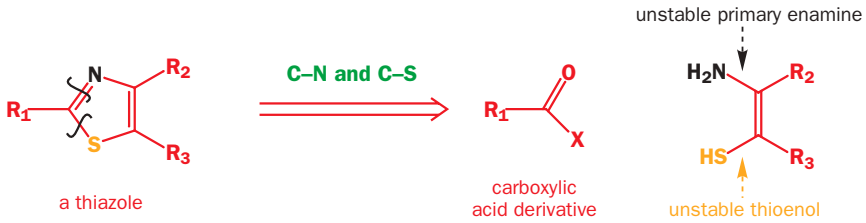


Condensation with ethyl formate (HCO_2Et) and cyclization with guanidine gives the pyrimidine ring system but with an OH instead of the required amino group. Aromatic nucleophilic substitution in the pyrimidone style from Chapter 43 gives trimethoprim.

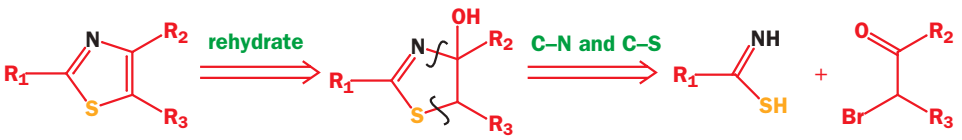


Unsymmetrical nucleophiles lead to selectivity questions

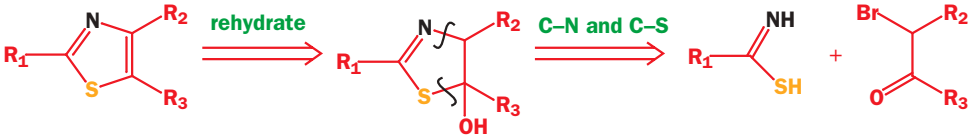
The synthesis of thiazoles is particularly interesting because of a regioselectivity problem. If we try out the two strategies we have just used for pyrimidines, the first requires the reaction of a carboxylic acid derivative with a most peculiar enamine that is also a thioenol. This does not look like a stable compound.



The alternative is to disconnect the C–N and C–S bonds on the other side of the heteroatoms. Here we must be careful what we are about or we will get the oxidation state wrong. We shall do it step by step to make sure. We can rehydrate the double bond in two ways. We can first try putting the OH group next to nitrogen.

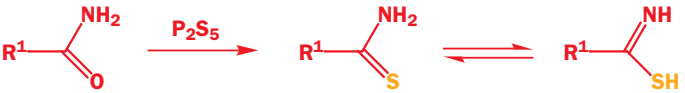


Or we can rehydrate it the other way round, putting the OH group next to the sulfur atom, and disconnect in the same way. In both cases we require an electrophilic carbon atom at the alcohol oxidation level and one at the aldehyde or ketone oxidation level. In other words we need an α-haloketone.



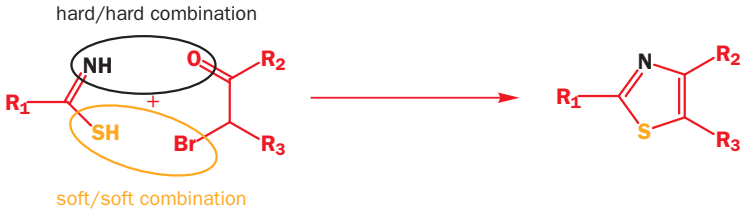
■ This is discussed in Chapter 46 and the structure of Lawesson's reagent is on p. 000 of that chapter.

The nucleophile is the same in both cases and it is an odd-looking molecule. That is, until we realize that it is just a tautomer of a thioamide. Far from being odd, thioamides are among the few stable thiocarbonyl derivatives and can be easily made from ordinary amides with P_2S_5 or Lawesson's reagent.

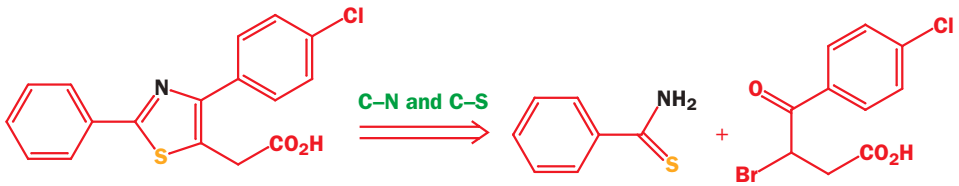


thioamide

So the only remaining question is: when thioamides combine with α-haloketones, which atom (N or S) attacks the ketone, and which atom (N or S) attacks the alkyl halide? Carbonyl groups are 'hard' electrophiles—their reactions are mainly under charge control and so they react best with basic nucleophiles (Chapter 12). Alkyl halides are 'soft' electrophiles—their reactions are mainly under frontier orbital control and they react best with large uncharged nucleophiles from the lower rows of the periodic table. The ketone reacts with nitrogen and the alkyl halide with sulfur.



Fentiazac, a nonsteroidal anti-inflammatory drug, is a simple example. Disconnection shows that we need thiobenzamide and an easily made α-haloketone (easily made because the ketone can enolize on this side only—see Chapter 21).



fentiazac

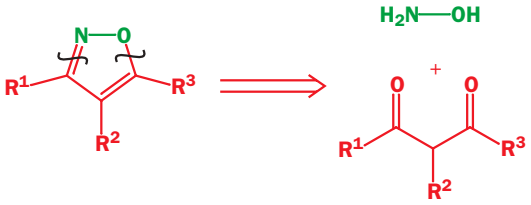
The synthesis involves heating these two compounds together and the correct thiazole forms easily with the double bonds finding their right positions in the product—the only positions for a stable aromatic heterocycle.

Isoxazoles are made from hydroxylamine or by 1,3-dipolar cycloadditions

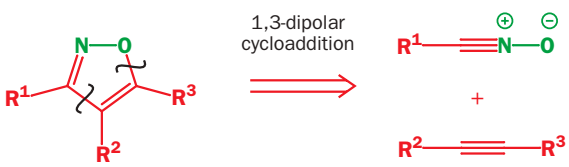
The two main routes for the synthesis of isoxazoles are the attack of hydroxylamine (NH_2OH) on diketones and 1,3-dipolar cycloadditions of nitrile oxides. They thus form a link between the strategy

we have been discussing (cyclization of a nucleophile with two heteroatoms and a compound with two electrophilic carbon atoms) and the next strategy—cycloaddition reactions.

strategy 1

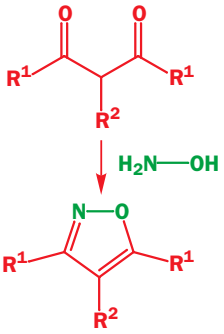


strategy 2

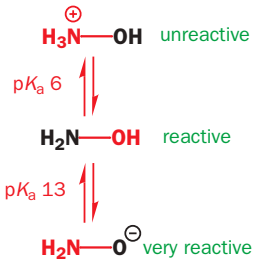


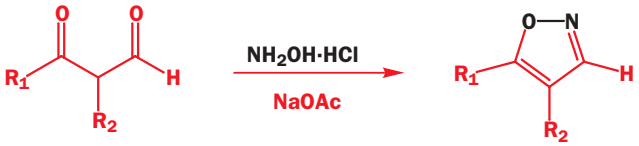
Simple symmetrical isoxazoles are easily made by the hydroxylamine route. If $R^1 = R^3$, we have a symmetrical and easily prepared 1,3-diketone as starting material. The central R^2 group can be inserted by alkylation of the stable enolate of the diketone (Chapter 26).

When $R^1 \neq R^3$, we have an unsymmetrical dicarbonyl compound and we must be sure that we know which way round the reaction will proceed. The more nucleophilic end of NH_2OH will attack the more electrophilic carbonyl group. It seems obvious that the more nucleophilic end of NH_2OH will be the nitrogen atom but that depends on the pH of the solution. Normally, hydroxylamine is supplied as the crystalline hydrochloride salt and a base of some kind added to give the nucleophile. The relevant pK_as are shown in the margin. Bases such as pyridine or sodium acetate produce some of the reactive neutral NH_2OH in the presence of the less reactive cation, but bases such as NaOEt produce the anion. Reactions of keto-aldehydes with acetate-buffered hydroxylamine usually give the isoxazole from nitrogen attack on the aldehyde as expected.

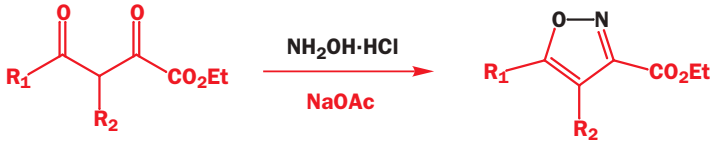


state of hydroxylamine changes with pH: the more nucleophilic atom is marked in black

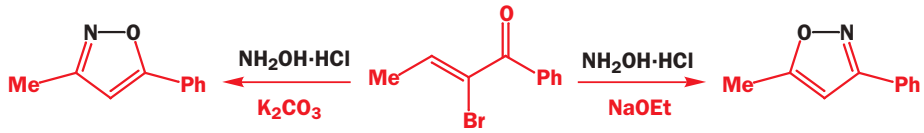




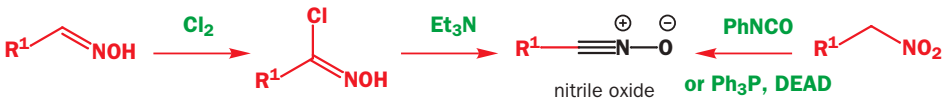
Modification of the electrophile may also be successful. Reaction of hydroxylamine with 1,2,4-diketo-esters usually gives the isoxazole from attack of nitrogen at the more reactive keto group next to the ester.



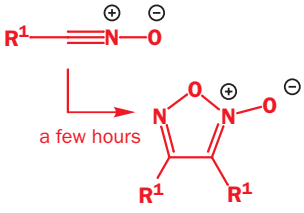
A clear demonstration of selectivity comes from the reactions of bromoenones. It is not immediately clear which end of the electrophile is more reactive but the reactions tell us the answer.

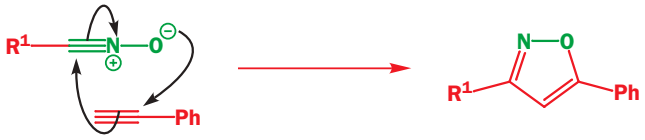


The alternative approach to isoxazoles relies on cycloadditions of nitrile oxides with alkynes. We saw in Chapter 35 that there are two good routes to these reactive compounds, the γ-elimination of chlorooximes or the dehydration of nitroalkanes.

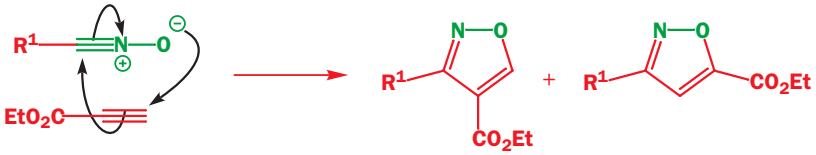


A few nitrile oxides are stable enough to be isolated (those with electron-withdrawing or highly conjugating substituents, for example) but most are prepared in the presence of the alkyne by one of these methods because otherwise they dimerize rapidly. Both methods of forming nitrile oxides are compatible with their rapid reactions with alkynes. Reaction with aryl alkynes is usually clean and regioselective.

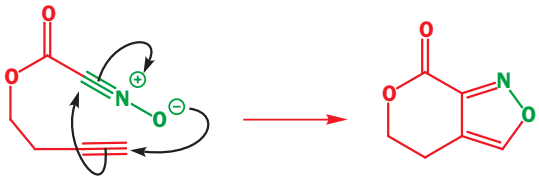




The alkyne is using its HOMO to attack the LUMO of the nitrile oxide (see Chapter 35 for an explanation). If the alkyne has an electron-withdrawing group, mixtures of isomers are usually formed as the HOMO of the nitrile oxide also attacks the LUMO of the alkyne.



Intramolecular reactions are usually clean regardless of the preferred electronic orientation if the tether is too short to allow any cyclization except one. In this example, even the more favourable orientation looks very bad because of the linear nature of the reacting species, but only one isomer is formed.



Tetrazoles are also made by 1,3-dipolar cycloadditions

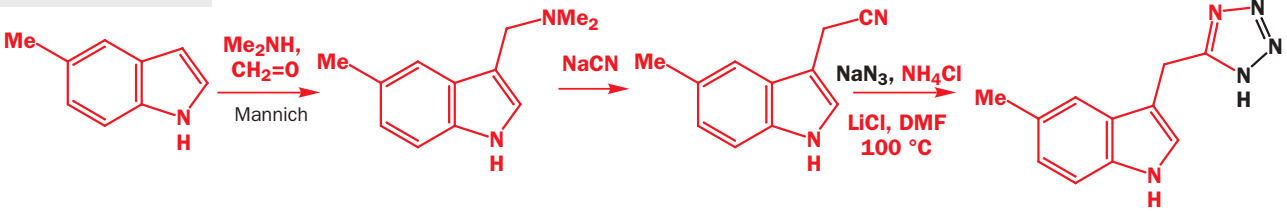
Disconnection of tetrazoles with a 1,3-dipolar cycloaddition in mind is easy to see once we realize that a nitrile (RCN) is going to be one of the components. It can be done in two ways: disconnection of the neutral compound would require hydrazoic acid (HN_3) as the dipole but the anion disconnects directly to azide ion.

■ You saw in Chapter 43 that tetrazoles are about as acidic as carboxylic acids.

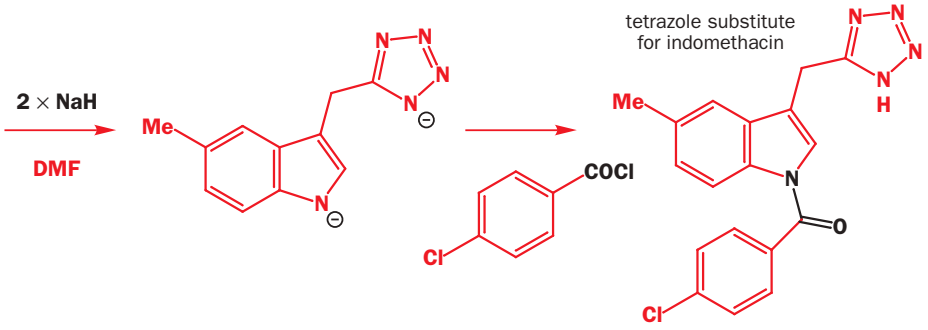
Unpromising though this reaction may look, it actually works well if an ammonium-chloride-buffered mixture of sodium azide and the nitrile is heated in DMF. The reagent is really ammonium azide and the reaction occurs faster with electron-withdrawing substituents in R. In the reaction mixture, the anion of the tetrazole is formed but neutralization with acid gives the free tetrazole.

As nitriles are generally readily available this is the main route to simple tetrazoles. More complicated ones are made by alkylation of the product of a cycloaddition. The tetrazole substitute for indomethacin that we mentioned in Chapter 43 is made by this approach. First, the nitrile is prepared from the indole. The 1,3-dipolar cycloaddition works well by the azide route we have just discussed, even though this nitrile will form an 'enol' rather easily.

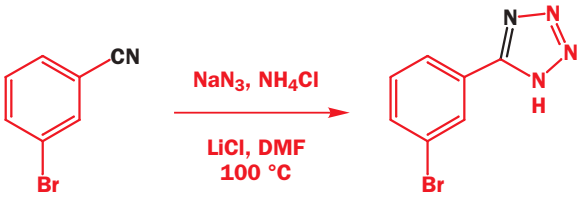
■ The synthesis of the indole starting material is in the next section.



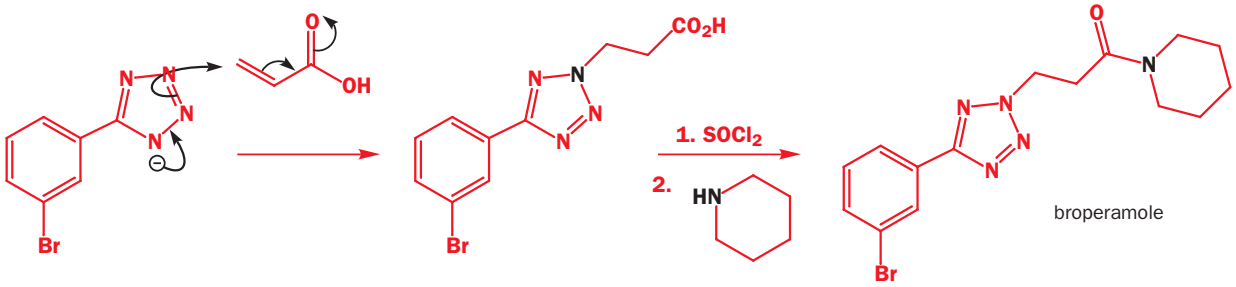
Finally, the indole nitrogen atom must be acylated. The tetrazole is more acidic so it is necessary to form a dianion to get reaction at the right place. The usual rule is followed (see Chapter 24)—the second anion formed is less stable and so it reacts first.



The synthesis of the anti-inflammatory drug broperamole illustrates modification of a tetrazole using its anion. The tetrazole is again constructed from the nitrile—it's an aromatic nitrile with an electron-withdrawing substituent so this will be a good reaction.

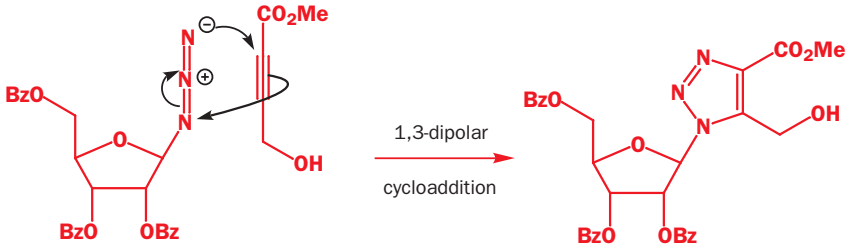


Conjugate addition to acrylic acid (Chapters 10 and 23) occurs to give the other tautomer to the one we have drawn. The anion intermediate is, of course, delocalized and can react at any of the nitrogen atoms. Amide formation completes the synthesis of broperamole.

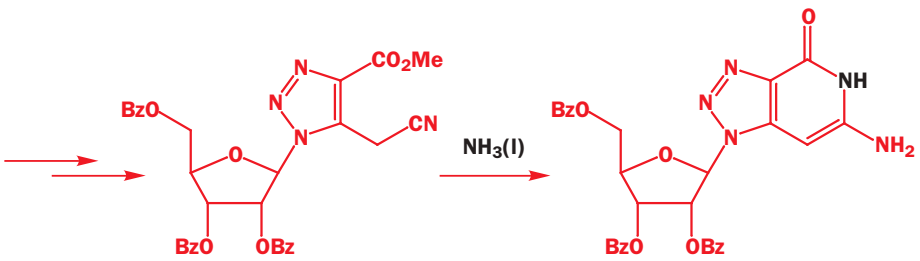


The difficulty in trying to forecast which way round a 1,3-dipolar cycloaddition will go is well illustrated when a substituted azide adds to an alkyne in the synthesis of 1,2,3-triazoles. Reaction of an alkyl azide with an unsymmetrical alkyne, having an electron-withdrawing group at one end and an alkyl group at the other, gives mostly a single triazole.

■ 1,2,4-Triazoles are usually made from the reaction of the unsubstituted 1,2,4-triazole anion with electrophiles as described in Chapter 43.



It looks as if the more nucleophilic end of the azide has attacked the wrong end of the alkyne but we must remember that (1) it is very difficult to predict which is the more nucleophilic end of a 1,3-dipole and (2) it may be either HOMO (dipole) and LUMO (alkyne) or LUMO (dipole) and HOMO (alkyne) that dominate the reaction. The reason for doing the reaction was to make analogues of natural nucleosides (the natural compounds are discussed in Chapter 49). In this case the OH group was replaced by a cyanide so that a second aromatic ring, a pyridine, can be fused on to the triazole.

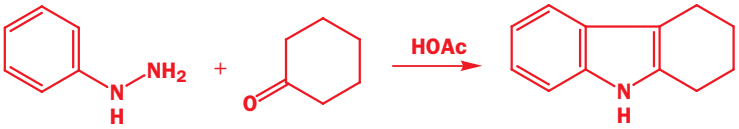


The next section deals with the synthesis of heterocycles where a heterocyclic ring is fused to a benzene ring, the 6/5 system, indole, and the 6/6 systems, quinoline and isoquinoline.

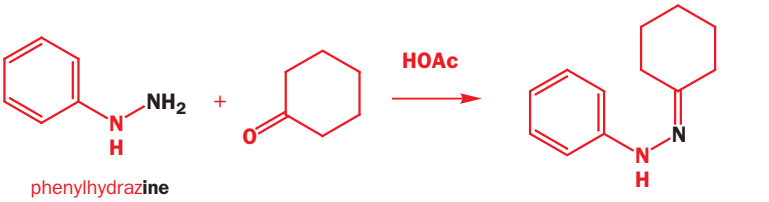
The Fischer indole synthesis

You are about to see one of the great inventions of organic chemistry. It is a remarkable reaction, amazing in its mechanism, and it was discovered in 1883 by one of the greatest organic chemists of all, Emil Fischer. Fischer had earlier discovered phenylhydrazine ($PhNHNH_2$) and, in its simplest form, the **Fischer indole synthesis** occurs when phenylhydrazine is heated in acidic solution with an aldehyde or ketone.

■ Emil Fischer (1852–1919), discovered phenylhydrazine as a PhD student in 1875, succeeded Hofmann at Berlin in 1900 where he built the then largest chemical institute in the world, and was awarded the Nobel prize in 1902. As well as his work on indoles, he laid the foundations of carbohydrate chemistry by completing the structure and synthesis of the main sugars. If only he hadn't also invented Fischer projections!



The first step in the mechanism is formation of the phenylhydrazone (the imine) of the ketone. This can be isolated as a stable compound (Chapter 14).

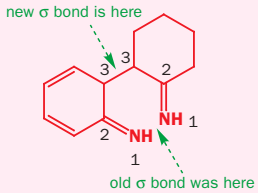


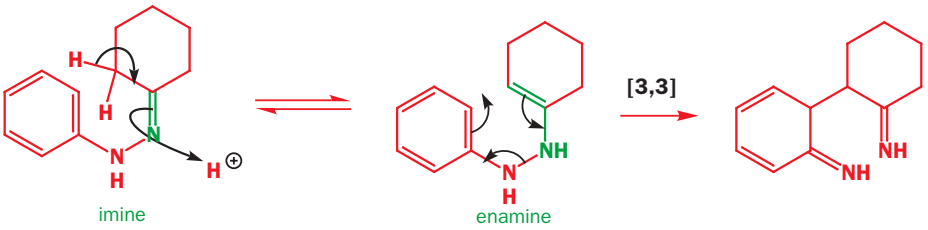
phenylhydrazine

cyclohexanone phenylhydrazone

The hydrazone then needs to tautomerize to the enamine, and now comes the key step in the reaction. The enamine can rearrange with formation of a strong C–C bond and cleavage of the weak N–N single bond by moving electrons round a six-membered ring.

▶ This step is a [3,3]-sigmatropic rearrangement (Chapter 36): the new single bond (C–C) bears a 3,3 relationship to the old single bond (N–N).

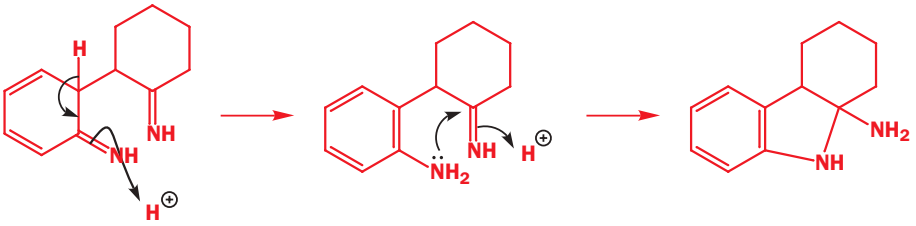




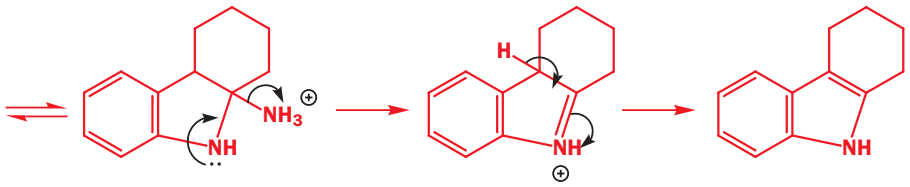
imine

enamine

Next, re-aromatization of the benzene ring (by proton transfer from carbon to nitrogen) creates an aromatic amine that immediately attacks the other imine. This gives an **aminal**, the nitrogen equivalent of an acetal.

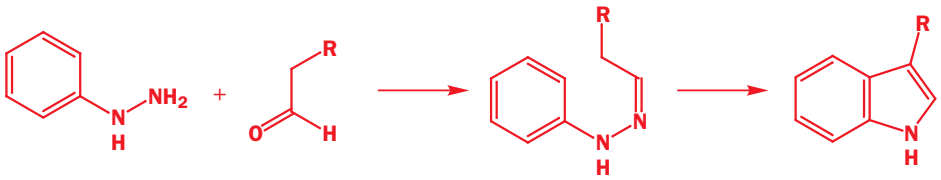


Finally, acid-catalysed decomposition of the aminal in acetal fashion with expulsion of ammonia allows the loss of a proton and the formation of the aromatic indole.

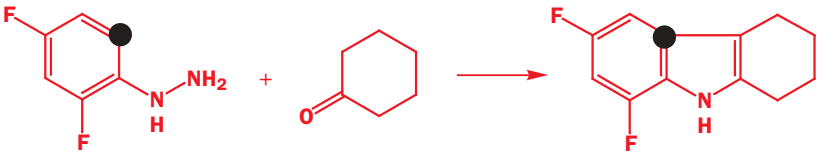


This is admittedly a complicated mechanism but if you remember the central step—the [3,3]-sigmatropic rearrangement—the rest should fall into place. The key point is that the C–C bond is established at the expense of a weak N–N bond. Naturally, Fischer had no idea about [3,3] or any other steps in the mechanism. He was sharp enough to see that something remarkable had happened and skilful enough to find out what it was.

The Fischer method is the main way of making indoles, but it is not suitable for them all. We need now to study its applicability to various substitution patterns. If the carbonyl compound can enolize on one side only, as is the case with an aldehyde, then the obvious product is formed.

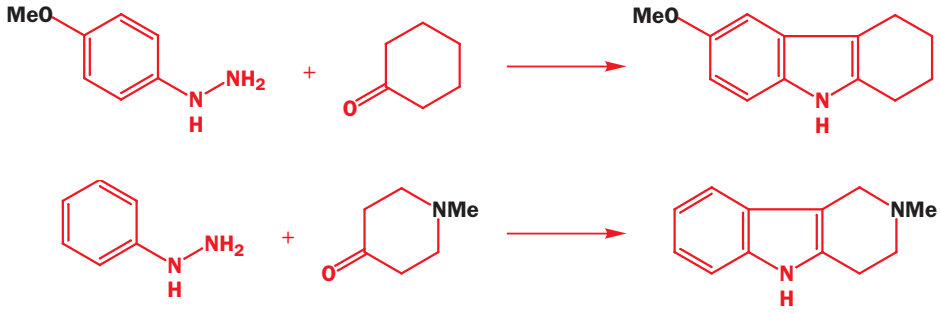


If the benzene ring has only one *ortho* position, then again cyclization must occur to that position. Other substituents on the ring are irrelevant. At this point we shall stop drawing the intermediate phenylhydrazone.

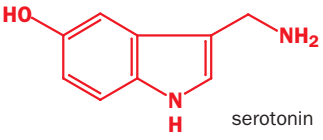


only one free *ortho* position

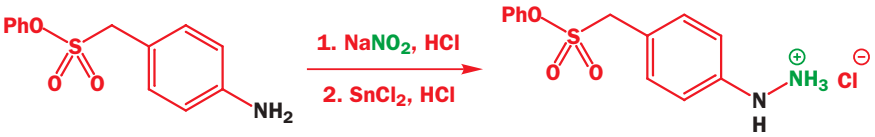
Another way to secure a single indole as product from the Fischer indole synthesis is to make sure the reagents are symmetrical. These two examples should make plain the types of indole available from symmetrical starting materials.



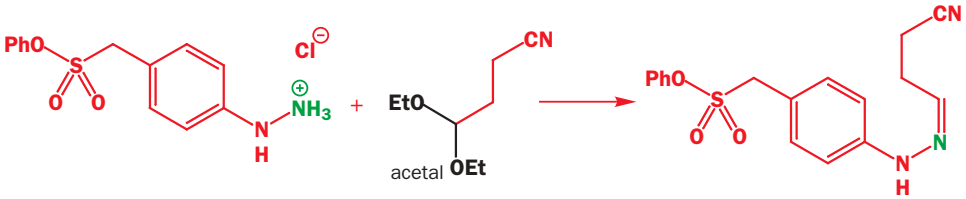
The substitution pattern of the first example is particularly important as the neurotransmitter serotonin is an indole with a hydroxyl group in the 5-position, and many important drugs follow that pattern. Sumatriptan (marketed as Imigran), is an example that we can also use to show that substituted phenylhydrazines are made by reduction of diazonium salts (Chapter 23). The first stage of the synthesis is nitrosation of the aniline and reduction with $SnCl_2$ and HCl to give the salt of the phenylhydrazine.



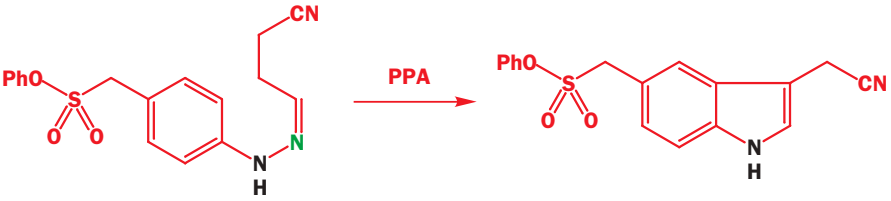
serotonin



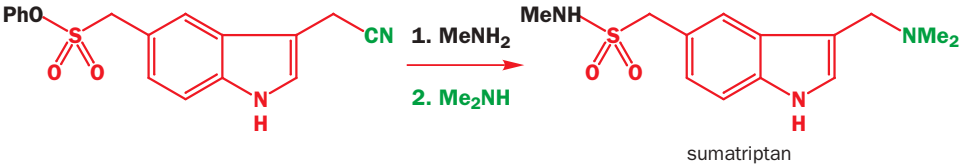
The required aldehyde (3-cyanopropanal) is added as an acetal to prevent self-condensation. The acidic conditions release the aldehyde, which forms the phenylhydrazone ready for the next step.



The Fischer indole synthesis itself is catalysed in this case by polyphosphoric acid (PPA), a sticky gum based on phosphoric acid (H_3PO_4) but dehydrated so that it contains some oligomers. It is often used as a catalyst in organic reactions and residues are easily removed in water.

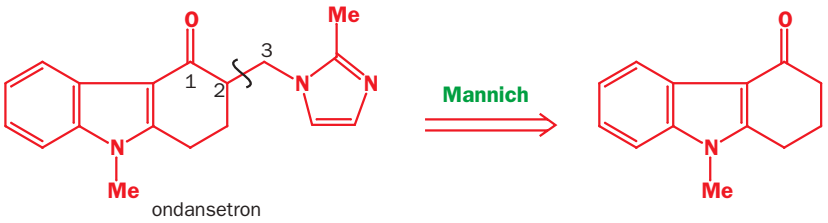


All that remains is to introduce the methyl amino and dimethylamino groups. The sulfonate ester is more reactive than the nitrile so the methyl amino group must go in first.



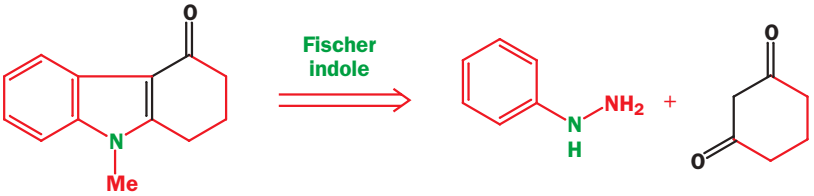
sumatriptan

For some indoles it is necessary to control regioselectivity with unsymmetrical carbonyl compounds. Ondansetron, the anti-nausea compound that is used to help cancer patients take larger doses of antitumour compounds than was previously possible, is an example. It contains an indole and an imidazole ring.

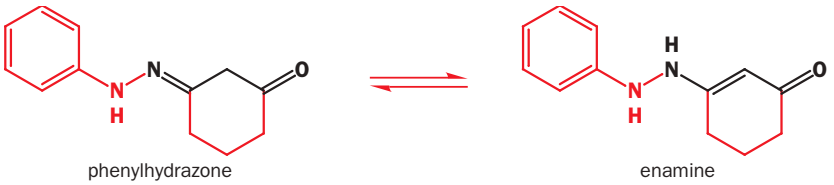


ondansetron

The 1,3 relationship between C–N and C–O suggests a Mannich reaction to add the imidazole ring (Chapter 27), and that disconnection reveals an indole with an unsymmetrical right-hand side, having an extra ketone group. Fischer disconnection will reveal a diketone as partner for phenylhydrazine. We shall leave aside for the moment when to add the methyl group to the indole nitrogen.

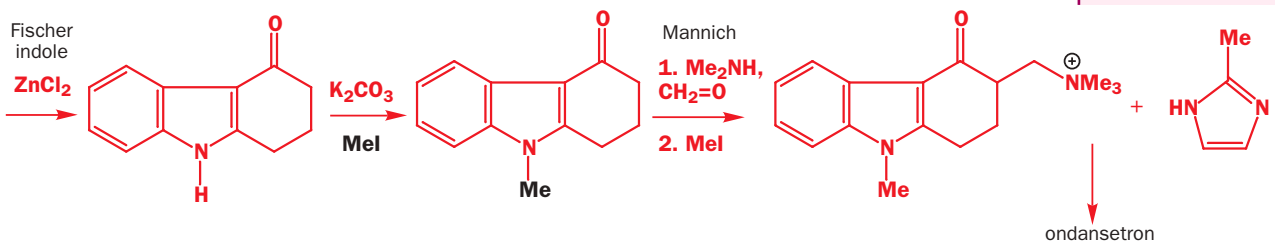


The diketone has two identical carbonyl groups and will enolize (or form an enamine) exclusively towards the other ketone. The phenylhydrazone therefore forms only the enamine we want.

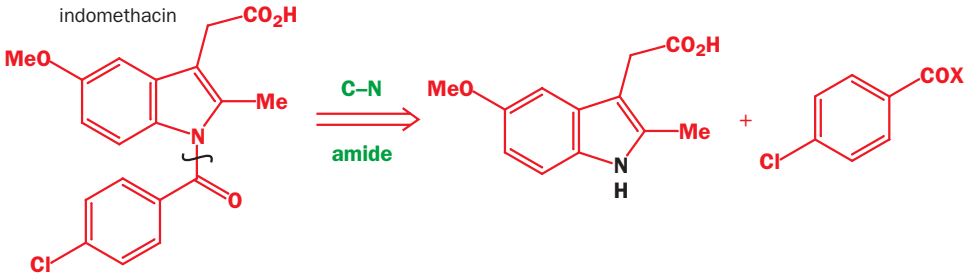


▶ Notice that we have drawn a different geometrical isomer of the imine from the one we have previously drawn and you might at first think that this one cannot cyclize. But the geometry of the phenylhydrazone is unimportant—you might like to think why.

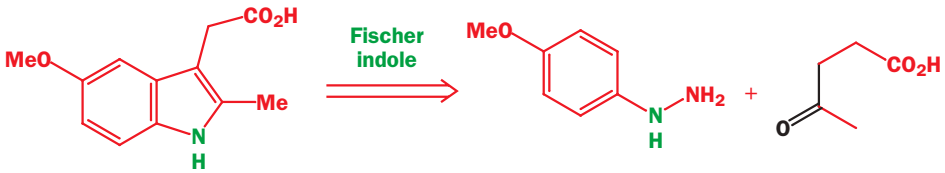
In this case, the Fischer indole reaction was catalysed by a Lewis acid, $ZnCl_2$, and base-catalysed methylation followed. The final stages are summarized below.



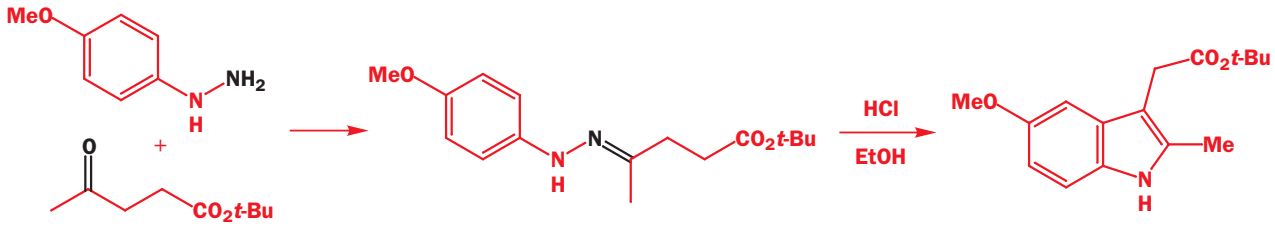
In the worst case, there is no such simple distinction between the two sites for enamine formation and we must rely on other methods of control. The nonsteroidal anti-inflammatory drug indomethacin is a good example. Removing the *N*-acyl group reveals an indole with substituents in both halves of the molecule.



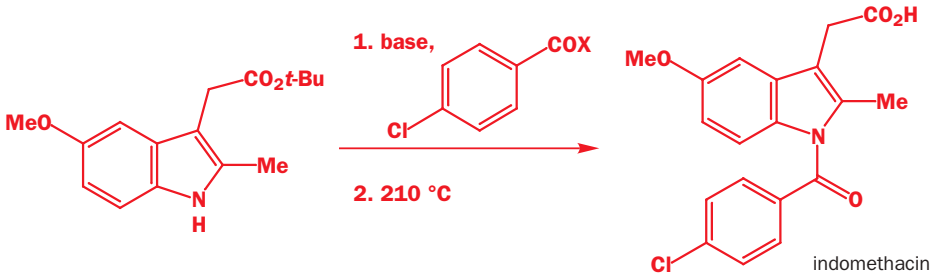
The benzene ring portion is symmetrical and is ideal for the Fischer synthesis but the right-hand half must come from an unsymmetrical open-chain keto-acid. Is it possible to control such a synthesis?



The Fischer indole is acid-catalysed so we must ask: on what side of the ketone is enolization (and therefore enamine formation) expected in acid solution? The answer is away from the methyl group and into the alkyl chain (Chapter 21). This is what we want and the reaction does indeed go this way. In fact, the *t*-butyl ester is used instead of the free acid.

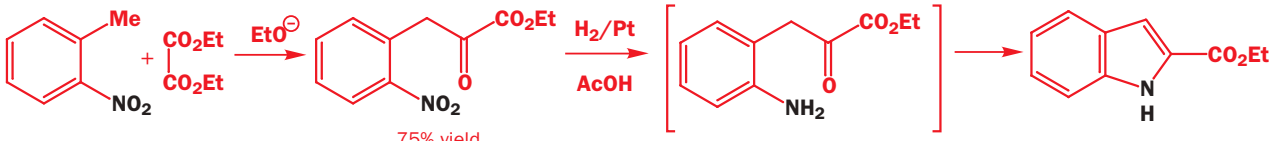


Acylation at the indole nitrogen atom is achieved with acid chloride in base and removal of the *t*-butyl ester gives free indomethacin.



indomethacin

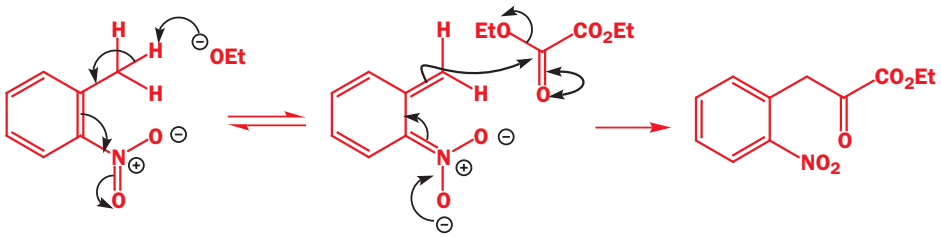
There are many other indole syntheses but we will give a brief mention to only one other and that is because it allows the synthesis of indoles with a different substitution pattern in the benzene ring. If you like names, you may call it the Reissert synthesis, and this is the basic reaction.



75% yield

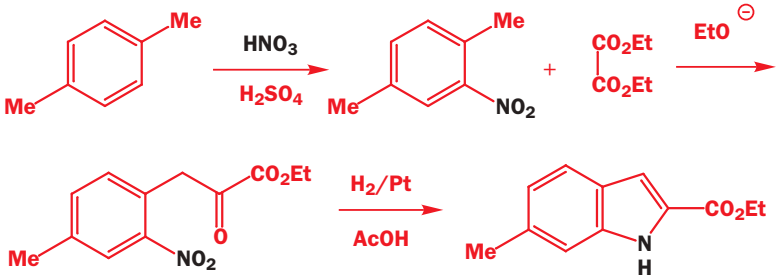
65% yield

Ethoxide is a strong enough base to remove a proton from the methyl group, delocalizing the negative charge into the nitro group. The anion then attacks the reactive diester (diethyl oxalate) and is acylated by it.



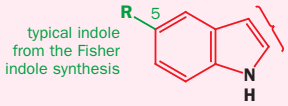
The rest of the synthesis is more straightforward: the nitro group can be reduced to an amine, which immediately forms an enamine by intramolecular attack on the more reactive carbonyl group (the ketone) to give the aromatic indole.

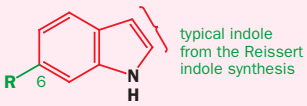
Since the nitro compound is made by nitration of a benzene ring, the preferred symmetry is very different from that needed for the Fischer synthesis. Nitration of *para*-xylene (1,4-dimethylbenzene) is a good example.

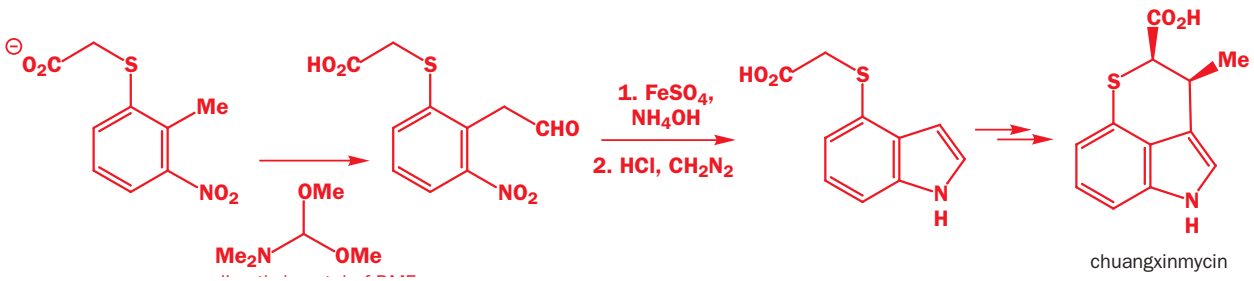


The ester products we have been using so far can be hydrolysed and decarboxylated by the mechanism described in the last chapter if a free indole is required. In any case, it is not necessary to use diethyl oxalate as the electrophilic carbonyl compound. The strange antibiotic chuangxinmycin (which you met in Chapter 32) was made by a Reissert synthesis using the acetal of DMF as the electrophile. Here is part of the synthesis.

▶ We can contrast the types of indole made by the Fischer and by the Reissert syntheses by the different ideal positions for substituents. These are, of course, not the only possible substitution patterns.

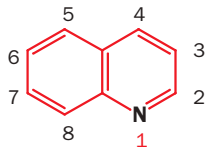


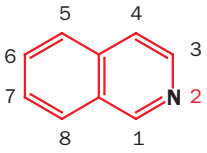




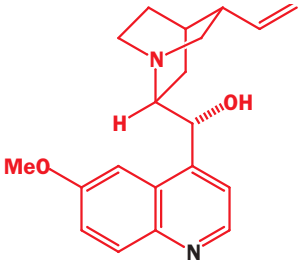
Quinolines and isoquinolines

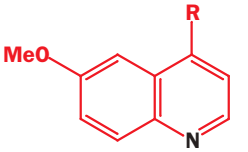
We move from benzo-fused pyrroles to benzo-fused pyridines and meet quinoline and isoquinoline. Isoquinolines will feature as benzylisoquinoline alkaloids in Chapter 51 and their synthesis will mostly be discussed there. In this section we shall concentrate on the quinolines.


quinoline

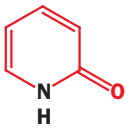

isoquinoline

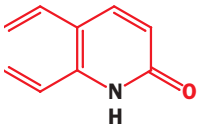
Quinoline forms part of the structure of quinine, the malaria remedy found in cinchona bark and known since the time of the Incas. The quinoline in quinine has a 6-MeO substituent and a side chain attached to C4. In discussing the synthesis of quinolines, we will be particularly interested in this pattern. This is because the search for anti-malarial compounds continues and other quinolines with similar structures are among the available anti-malarial drugs.

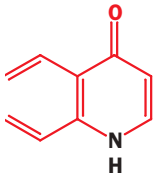

quinine

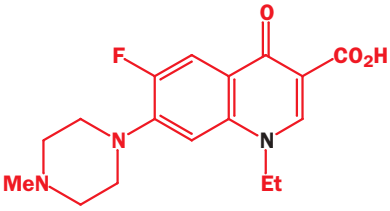

the quinoline in quinine

We shall also be very interested in quinolones, analogous to pyridones, with carbonyl groups at positions 2 and 4 as these are useful antibiotics. A simple example is pefloxacin which has a typical 6-F and 7-piperazine substituents.

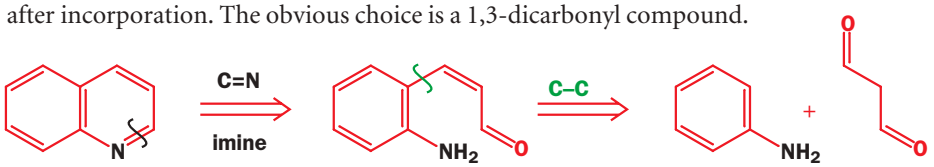

2-pyridone


2-quinolone

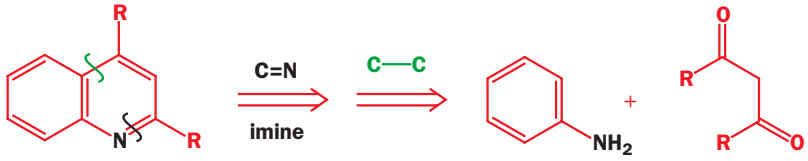

4-quinolone


a quinolone antibiotic, pefloxacin

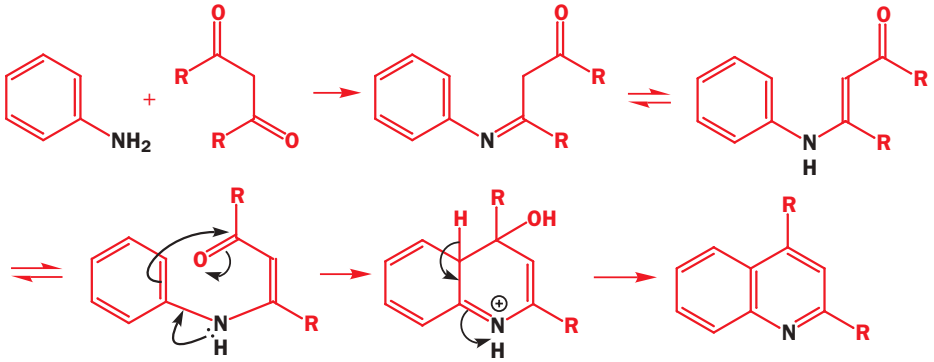
When we consider the synthesis of a quinoline, the obvious disconnections are, first, the C–N bond in the pyridine ring and, then, the C–C bond that joins the side chain to the benzene ring. We will need a three-carbon (C_3) synthon, electrophilic at both ends, which will yield two double bonds after incorporation. The obvious choice is a 1,3-dicarbonyl compound.



The choice of an aromatic amine is a good one as the NH_2 group reacts well with carbonyl compounds and it activates the *ortho* position to electrophilic attack. However, the dialdehyde is malonic dialdehyde, a compound that does not exist, so some alternative must be found. If the quinoline is substituted in the 2- and 4-positions this approach looks better.



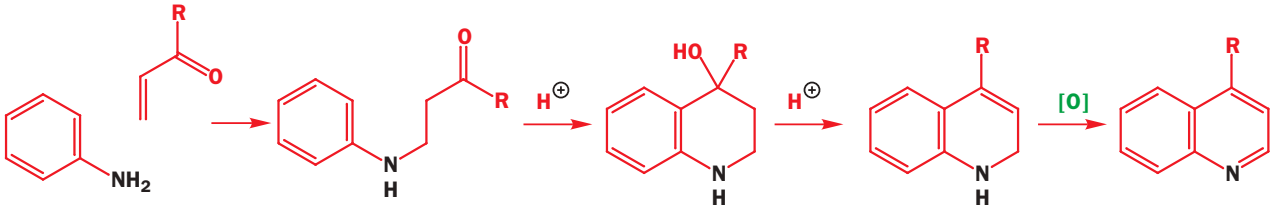
The initially formed imine will tautomerize to a conjugated enamine and cyclization now occurs by electrophilic aromatic substitution.



The enamine will normally prefer to adopt the first configuration shown in which cyclization is not possible, and (perhaps for this reason or perhaps because it is difficult to predict which quinoline will be formed from an unsymmetrical 1,3-dicarbonyl compound) this has not proved a very important quinoline synthesis. We shall describe two more important variants on the same theme, one for quinolines and one for quinolones.

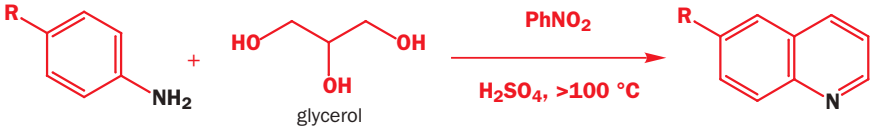
In the synthesis of pyridines it proved advantageous to make a dihydropyridine and oxidize it to a pyridine afterwards. The same idea works well in probably the most famous quinoline synthesis, the **Skraup reaction**. The diketone is replaced by an unsaturated carbonyl compound so that the quinoline is formed regiospecifically.

The first step is conjugate addition of the amine. Under acid catalysis the ketone now cyclizes in the way we have just described to give a dihydroquinoline after dehydration. Oxidation to the aromatic quinoline is an easy step accomplished by many possible oxidants.

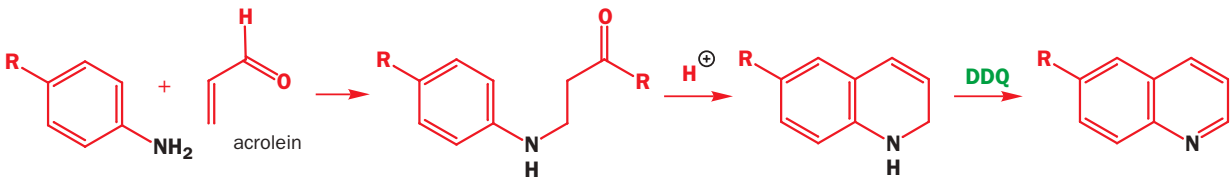


▶ The ugly name of the Skraup reaction appropriately applies to the worst 'witch's brew' of all the heterocyclic syntheses. Some workers have added strange oxidizing agents such as arsenic acid, iron (III) salts, tin (IV) salts, nitrobenzenes of various substitution patterns, or iodine to make it 'go better'.

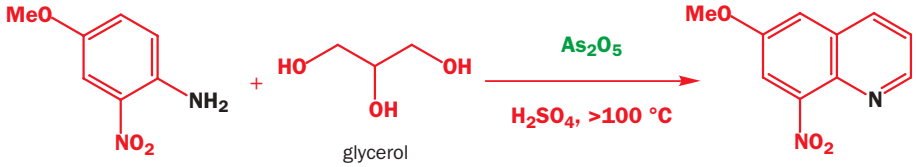
Traditionally, the Skraup reaction was carried out by mixing everything together and letting it rip. A typical mixture to make a quinoline without substituents on the pyridine ring would be the aromatic amine, concentrated sulfuric acid, glycerol, and nitrobenzene all heated up in a large flask at over 100 °C with a wide condenser.



The glycerol was to provide acrolein (CH_2=CH·CHO) by dehydration, the nitrobenzene was to act as oxidant, and the wide condenser...? All too often Skraup reactions did let rip—with destructive results. A safer approach is to prepare the conjugate adduct first, cyclize it in acid solution, and then oxidize it with one of the reagents we described for pyridine synthesis, particularly quinones such as DDQ.

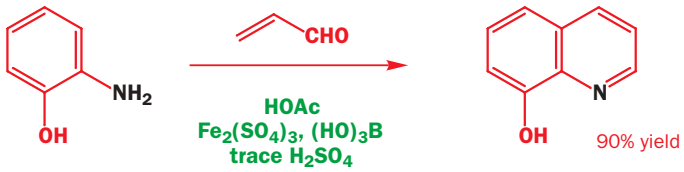


An important use of the traditional Skraup synthesis is to make 6-methoxy-8-nitroquinoline from an aromatic amine with only one free *ortho* position, glycerol, the usual concentrated sulfuric acid, and the oxidant arsenic pentoxide. Though the reported procedure uses 588 grams of As_2O_5, which might disconcert many chemists, it works well and the product can be turned into other quinolines by reduction of the nitro group, diazotization, and nucleophilic substitution (Chapter 23).

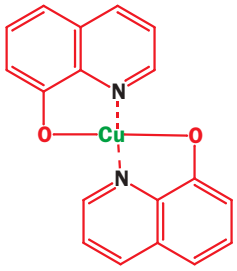


▶ Arsenic has a bad reputation because it is traditionally used by poisoners. If arsenic gets into living things it is indeed very poisonous—about 6 mg per kg is needed to kill an animal. However, many other compounds are equally toxic, but you just have to avoid eating them.

The more modern style of Skraup synthesis is used to make 8-quinolinol or 'oxine'. *ortho*-Aminophenol has only one free position *ortho* to the amino group and is very nucleophilic, so acrolein can be used in weak acid with only a trace of strong acid. Iron(III) is the oxidant with a bit of boric acid for luck, and the yield is excellent.



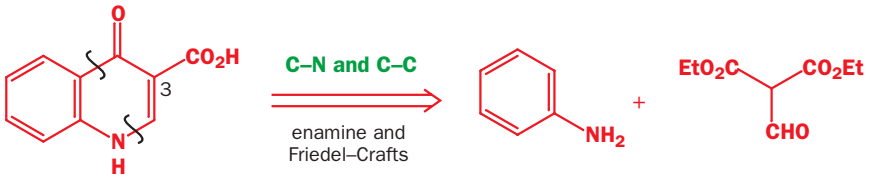
oxine complex of copper



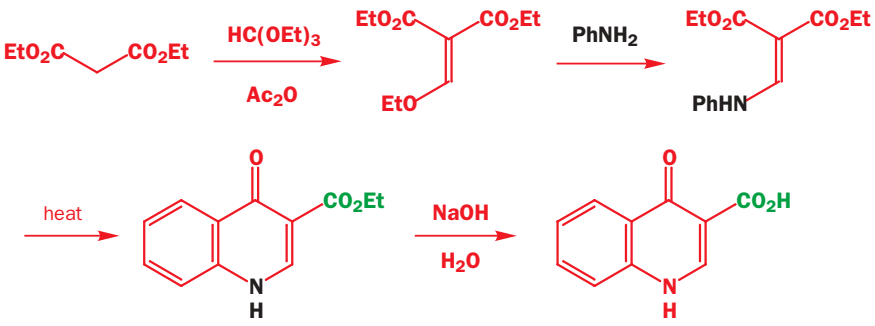
This compound is important because it forms unusually stable metal complexes with metal ions such as Mg(II) or Al(III). It is also used as a corrosion inhibitor on copper because it forms a stable layer of Cu(II) complex that prevents oxidation of the interior.

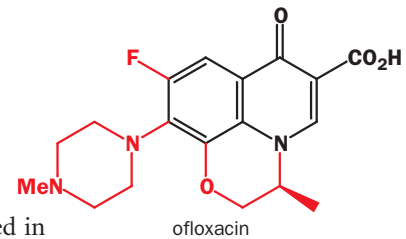
Quinolones also come from anilines by cyclization to an *ortho* position

The usual method for making quinolone antibiotics is possible because they all have a carboxylic acid in the 3-position. Disconnection suggests a rather unstable malonic ester derivative as starting material.



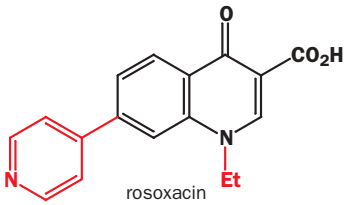
In fact, the enol ether of this compound is easily made from diethyl malonate and ethyl orthoformate [$HC(OEt)_3$]. The aromatic amine reacts with this compound by an addition–elimination sequence giving an enamine that cyclizes on heating. This time there is no worry about the geometry of the enamine.





ofloxacin

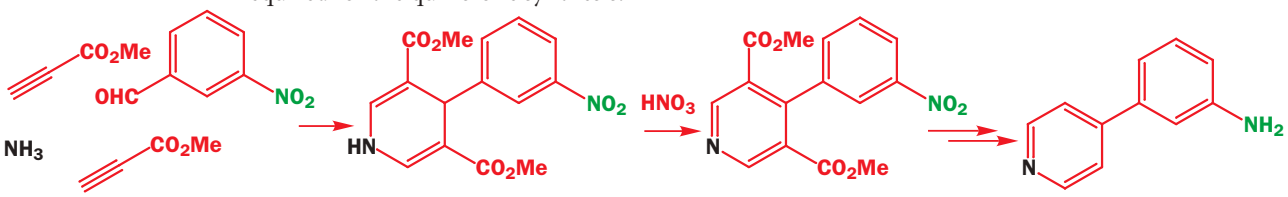
For examples of quinolone antibiotics we can choose ofloxacin, whose synthesis is discussed in detail in Chapter 23, and rosoxacin whose synthesis is discussed overleaf. Both molecules contain the



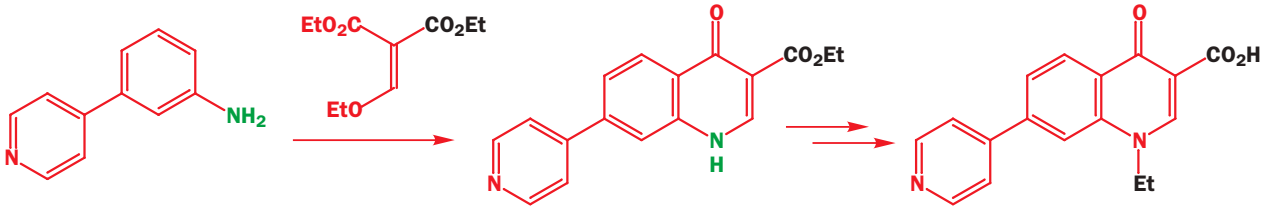
rosoxacin

same quinolone carboxylic acid framework, outlined in black, with another heterocyclic system at position 7 and various other substituents here and there.

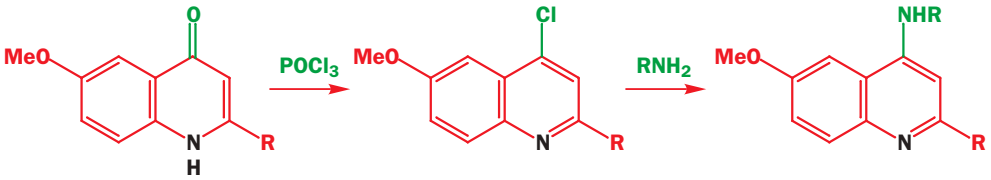
To make rosoxacin two heterocyclic systems must be constructed. Workers at the pharmaceutical company Sterling decided to build the pyridine in an ingenious version of the Hantzsch synthesis using acetylenic esters on 3-nitrobenzaldehyde. The ammonia was added as ammonium acetate. Oxidation with nitric acid made the pyridine, hydrolysis of the esters and decarboxylation removed the acid groups, and reduction with Fe(II) and HCl converted the nitro group into the amino group required for the quinolone synthesis.



Now the quinolone synthesis can be executed with the same reagents we used before and all that remains is ester hydrolysis and alkylation at nitrogen. Notice that the quinolone cyclization could in theory have occurred in two ways as the two positions *ortho* to the amino group are different. In practice cyclization occurs away from the pyridine ring as the alternative quinolone would be impossibly crowded.

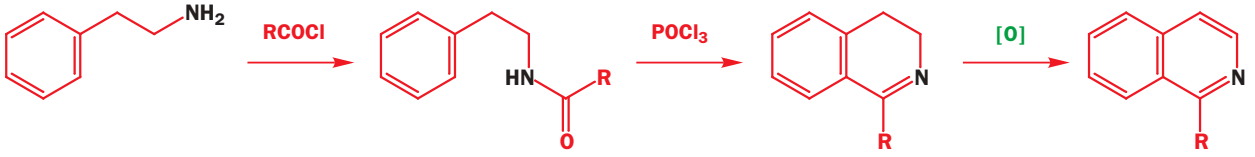


Since quinolones, like pyridones, can be converted into chloro-compounds with $POCl_3$, they can be used in nucleophilic substitution reactions to build up more complex quinolines.



▶ This dehydrogenation is the reverse of palladium-catalysed hydrogenation.

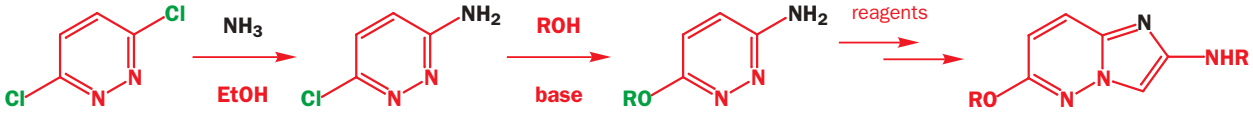
Because isoquinolines are dealt with in more detail in Chapter 51, we will give just one important synthesis here. It is a synthesis of a dihydroisoquinoline by what amounts to an intramolecular Vilsmeier reaction in which the electrophile is made from an amide and $POCl_3$. Since, to make the isoquinoline, two hydrogen atoms must be removed from carbon atoms it makes more sense to use a noble metal such as Pd(0) as the oxidizing agent rather than the reagents we used for pyridine synthesis.



More heteroatoms in fused rings mean more choice in synthesis

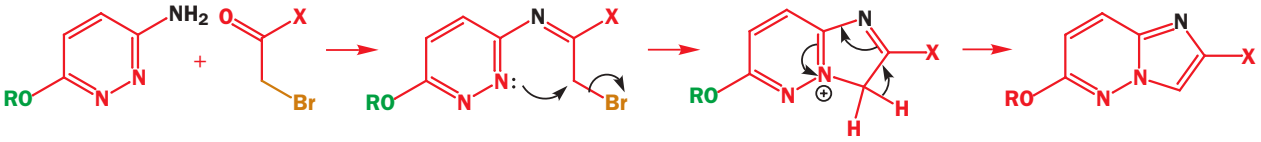
The imidazo-pyridazine ring system forms the basis for a number of drugs in human and animal medicine. The synthesis of this system uses chemistry discussed in Chapter 43 to build the pyridazine ring. There we established that it was easy to make dichloropyridazines and to displace the chlorine

atoms one by one with different nucleophiles. Now we will move on from these intermediates to the bicyclic system.

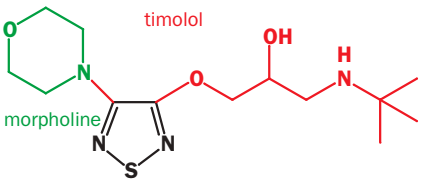


Imidazo[1,2-*b*]pyridazine

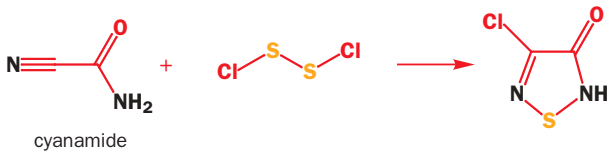
A 2-bromo-acid derivative is the vital reagent. It reacts at the amino nitrogen atom with the carbonyl group and at the pyridazine ring nitrogen atom with the alkyl halide. This is the only way the molecule can organize itself into a ten-electron aromatic system.



In Chapter 43 we also gave the structure of timolol, a thiadiazole-based β-blocker drug for reduction of high blood pressure. This compound has an aromatic 1,2,5-thiadiazole ring system and a saturated morpholine as well as an aliphatic side chain. Its synthesis relies on ring formation by rather a curious method followed by selective nucleophilic substitution, rather in the style of the last synthesis. The aromatic ring is made by the action of S_2Cl_2 on 'cyanamide'.

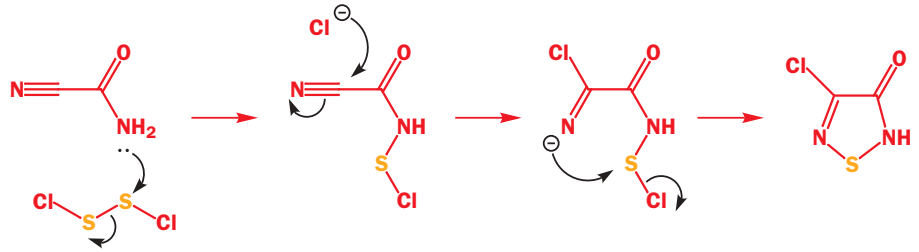


1,2,5-thiadiazole

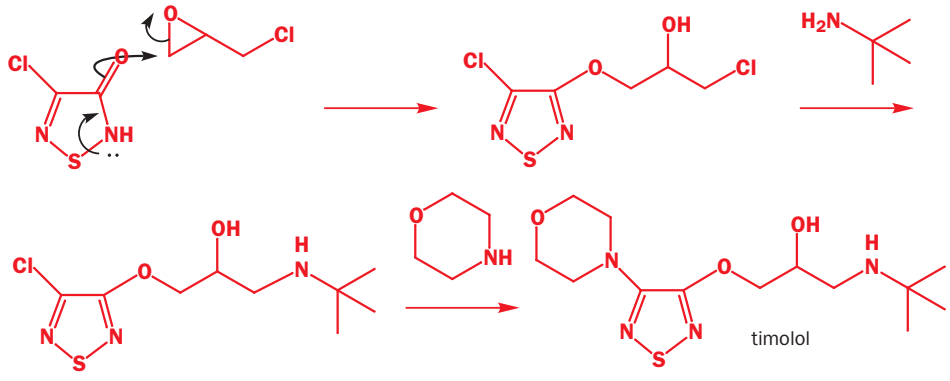


cyanamide

This reaction must start by attack of the amide nitrogen on the electrophilic sulfur atom. Cyclization cannot occur while the linear nitrile is in place so chloride ion must first attack CN. Thereafter cyclization is easy. The chloride ion probably comes from disproportionation of ClS^-.



Reaction with epichlorohydrin (the chloroepoxide shown below) followed by amine displacement puts in one of the side chains and nucleophilic substitution with morpholine on the ring completes the synthesis.



Summary: the three major approaches to the synthesis of aromatic heterocycles

We end this chapter with summaries of the three major strategies in the synthesis of heterocycles:

- ring construction by ionic reactions
- ring construction by pericyclic reactions
- modification of existing rings by electrophilic or nucleophilic aromatic substitution or by lithiation and reaction with electrophiles

We will summarize the different applications of these strategies, and also suggest cases for which each strategy is not suitable. This section revises material from Chapter 43 as well since most of the ring modifications appear there.

▶ This is only a summary. There are more details in the relevant sections of Chapters 43 and 44. There are also many, many more ways of making all these heterocycles. These methods are just where we suggest you *start*.

Ring construction by ionic cyclization

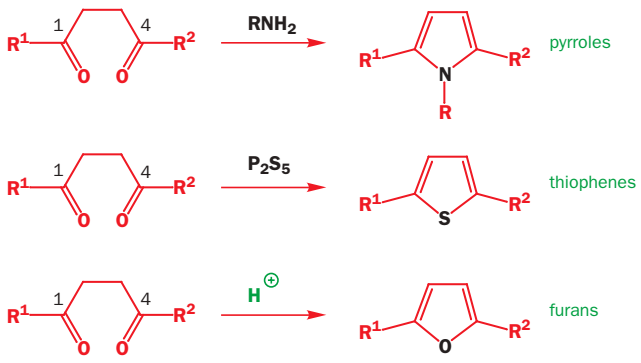
The first strategy you should try out when faced with the synthesis of an aromatic heterocyclic ring is the disconnection of bonds between the heteroatom or atoms and carbon, with the idea of using the heteroatoms as nucleophiles and the carbon fragment as a double electrophile.

Heterocycles with one heteroatom

five-membered rings

pyrroles, thiophenes, and furans

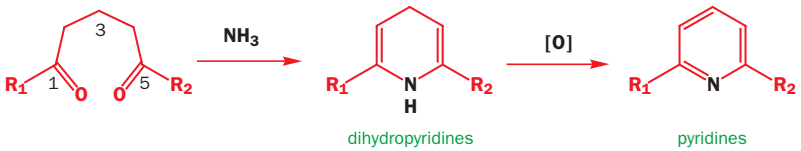
ideally made by this strategy from 1,4-dicarbonyl compounds



six-membered rings

pyridines

made by this strategy from 1,5-dicarbonyl compounds with oxidation

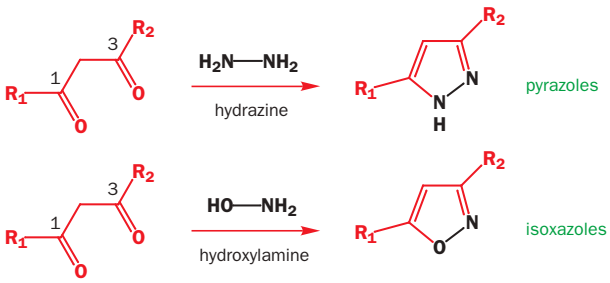


Heterocycles with two adjacent heteroatoms

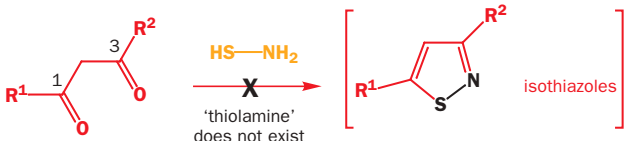
five-membered rings

pyrazoles and isoxazoles

ideally made by this strategy from 1,3-dicarbonyl compounds



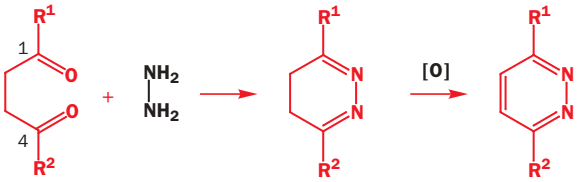
Note. This strategy is *not* suitable for isothiazoles as 'thiolamine' does not exist



six-membered rings

pyridazines

ideally made by this strategy from 1,4-dicarbonyl compounds with oxidation

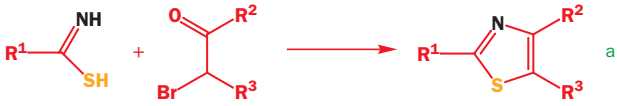


Heterocycles with two non-adjacent heteroatoms

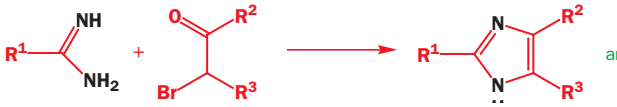
five-membered rings

imidazoles and thiazoles

ideally made by this strategy from α-halocarbonyl compound

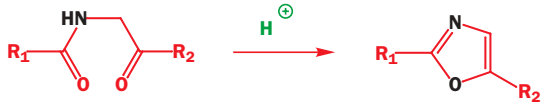


a thiazole



an imidazole

Note. This strategy is *not* suitable for oxazoles as amides are not usually reactive enough: cyclization of acylated carbonyl compounds is usually preferred

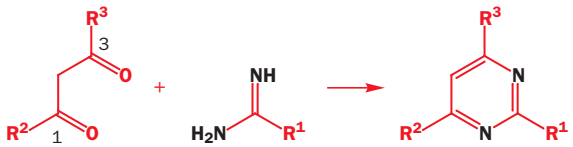


an oxazole

six-membered rings

pyrimidines

ideally made by this strategy from 1,3-dicarbonyl compounds



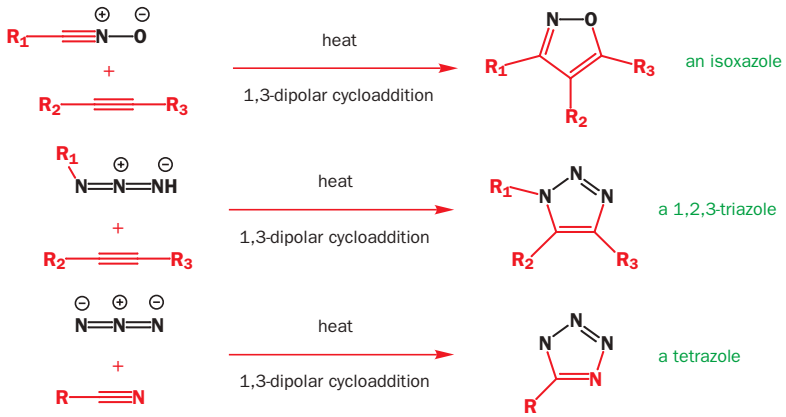
an amidine

a pyrimidine

Ring construction by pericyclic reactions

Cycloaddition reactions

1,3-dipolar cycloaddition is ideal for the construction of isoxazoles, 1,2,3-triazoles, and tetrazoles



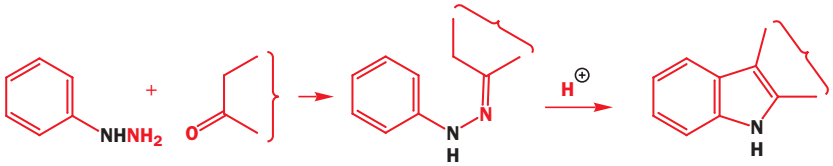
an isoxazole

a 1,2,3-triazole

a tetrazole

Sigmatropic rearrangements

a special reaction that is the vital step of the Fischer indole synthesis



phenylhydrazine

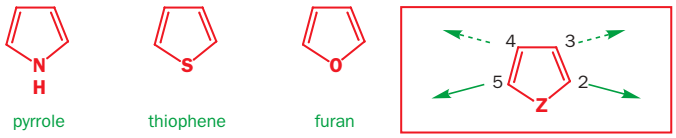
a phenylhydrazone

an indole

Ring modification

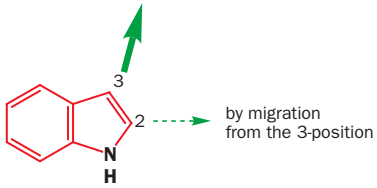
Electrophilic aromatic substitution

works very well on pyrroles, thiophenes and furans where it occurs best in the 2- and 5-positions and nearly as well in the 3- and 4-positions. Often best to block positions where substitution not wanted



pyrrole thiophene furan

works well for indole—occurs only in the 3-position but the electrophile may migrate to the 2-position



indole

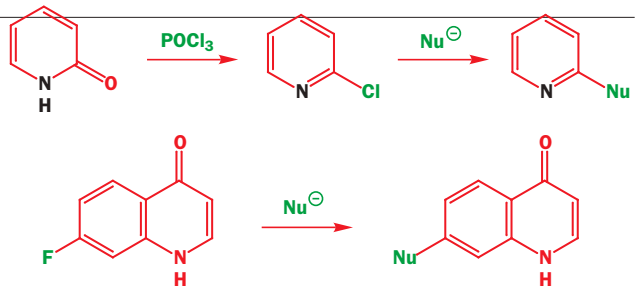
works well for five-membered rings with a sulfur, oxygen, or pyrrole-like nitrogen atom and occurs anywhere that is not
blocked (see earlier sections)

Note. *Not* recommended for pyridine, quinoline, or isoquinoline

Nucleophilic aromatic substitution

works particularly well for pyridine and quinoline where the charge in the intermediate can rest on nitrogen

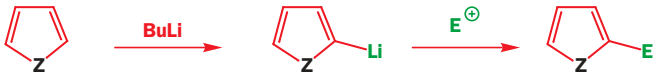
especially important for pyridones and quinolones with conversion to the chloro-compound and displacement of chlorine by nucleophiles and, for quinolines, displacement of fluorine atoms on the benzene ring



works well for the six-membered rings with two nitrogens (pyridazines, pyrimidines, and pyrazines) in all positions

Lithiation and reaction with electrophiles

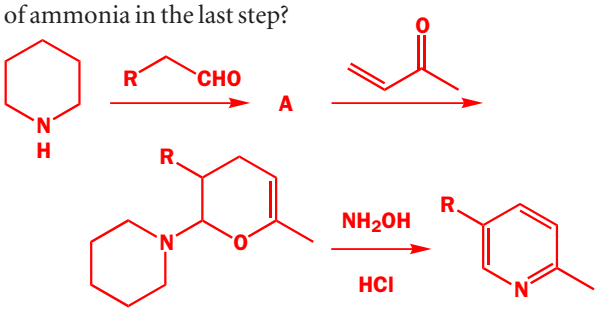
works well for pyrrole (if NH blocked), thiophene, or furan next to the heteroatom. Exchange of Br or I for Li works well for most electrophiles providing any acidic hydrogens (including the NH in the ring) are blocked



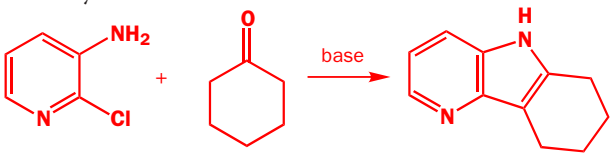
Z = NR, S, or O

Problems

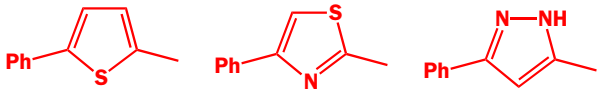
1. In this pyridine synthesis, give a structure for A and mechanisms for the reactions. Why is hydroxylamine used instead of ammonia in the last step?



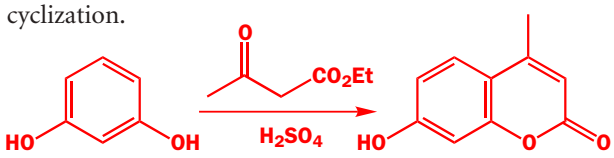
2. Suggest a mechanism for this synthesis of a tricyclic aromatic heterocycle.



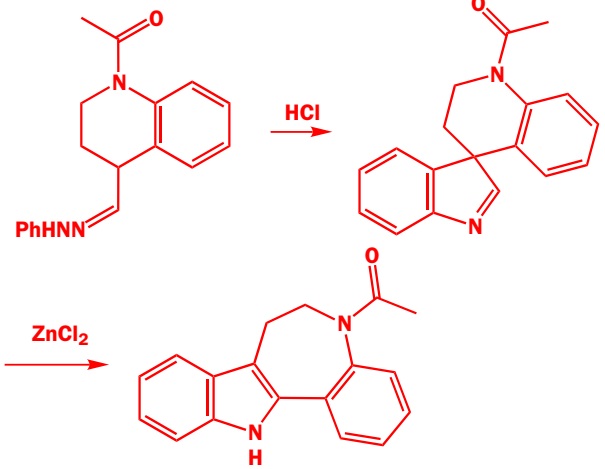
3. How would you synthesize these aromatic heterocycles?



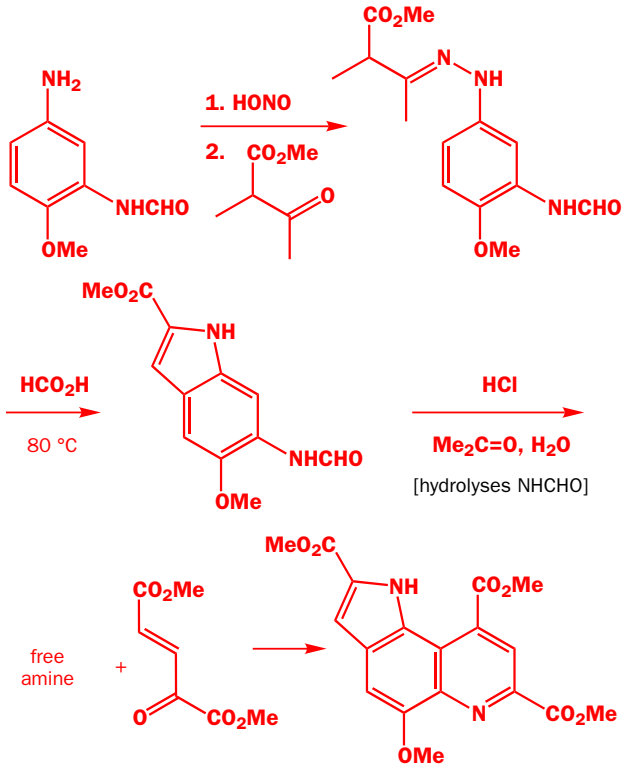
4. Is the heterocyclic ring created in this reaction aromatic? How does the reaction proceed? Comment on the selectivity of the cyclization.



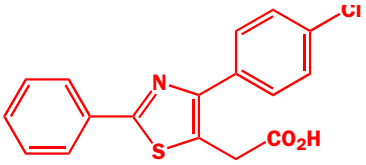
5. Suggest mechanisms for this unusual indole synthesis. How does the second reaction relate to electrophilic substitution at indoles as discussed in Chapter 33?



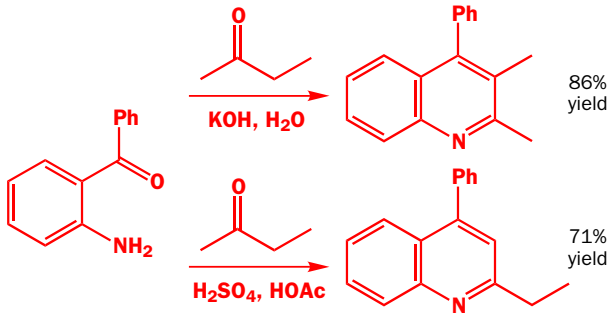
6. Explain the reactions in this partial synthesis of methoxatin, the coenzyme of bacteria living on methanol.



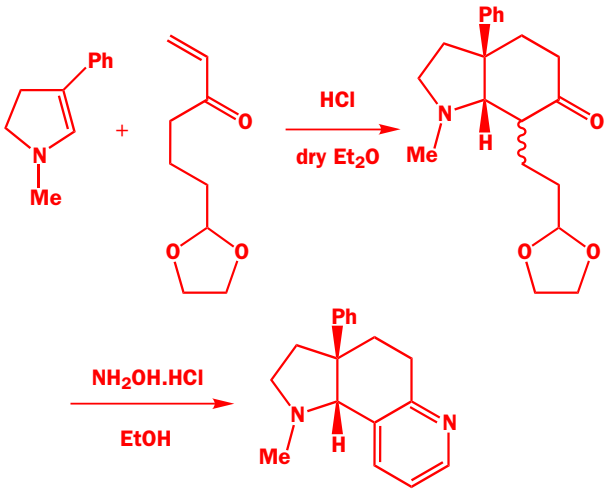
7. Suggest a synthesis of fentiazac, a nonsteroidal anti-inflammatory drug. The analysis is in the chapter but you need to explain why you need these particular starting materials as well as how you would make them.



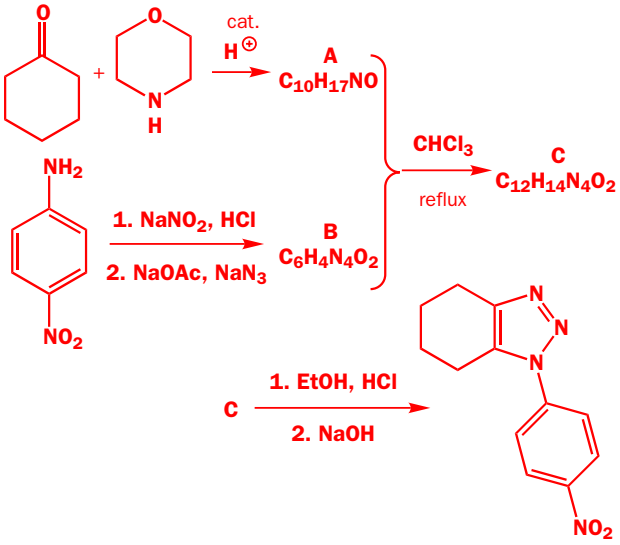
8. Explain why these two quinoline syntheses from the same starting materials give (mainly) different products.



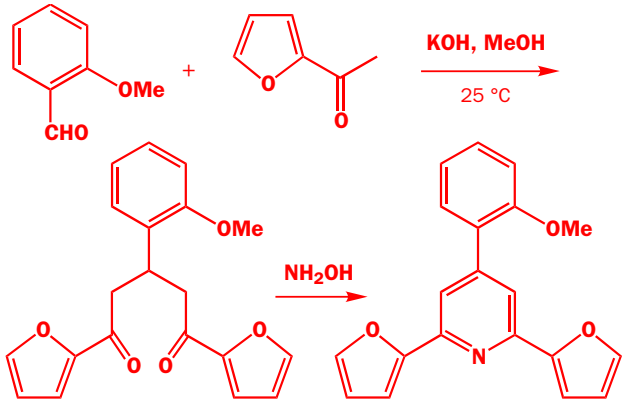
9. Give mechanisms for these reactions used to prepare a fused pyridine. Why is it necessary to use a protecting group?



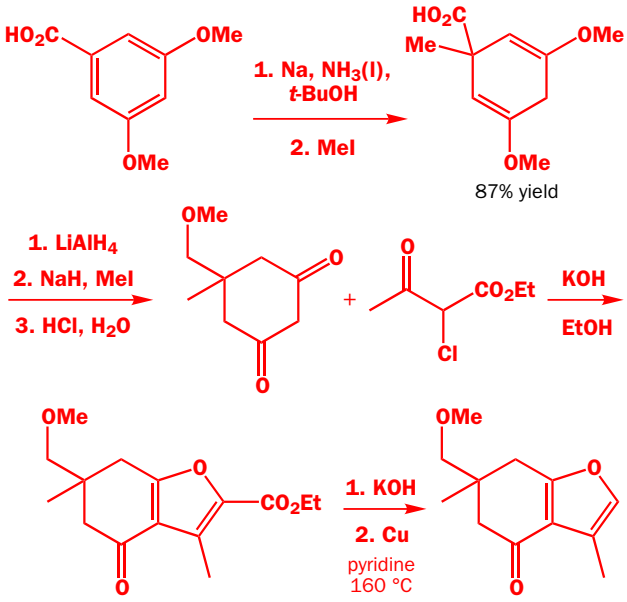
10. Identify the intermediates and give mechanisms for the steps in this synthesis of a triazole.



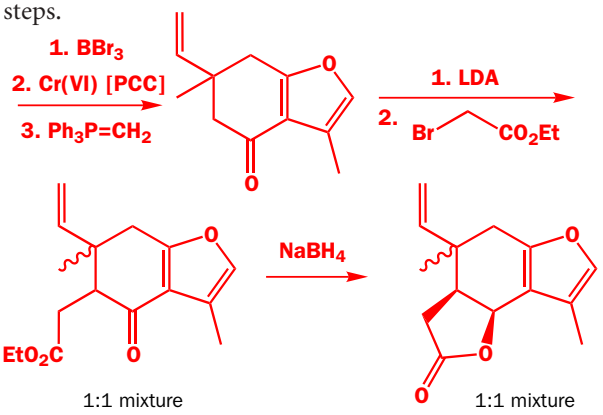
11. Give detailed mechanisms for this pyridine synthesis. The first part revises Chapters 27 and 29.



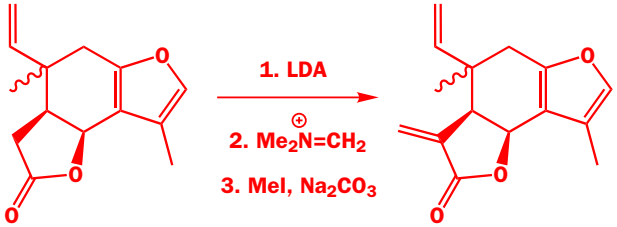
12. This question revises a number of previous chapters, especially 24–26, and 39. Give mechanisms for the reactions in this synthesis of a furan and comment on the choice of reagents for the various steps.



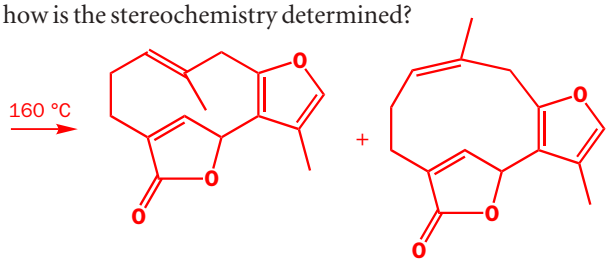
13. This question shows the purpose of making the furan in Problem 12 and revises material from Chapters 33 and 36. The above furan was used in the synthesis of the natural product linderalactone by first alkylation and reduction. Give mechanisms for the reactions and comment on the stereochemistry of these steps.



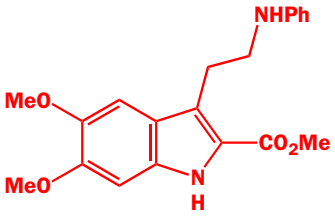
A version of the Mannich reaction on this lactone then gave an unsaturated compound that is still a 1:1 mixture of diastereoisomers. Give mechanisms for these reactions.



Each diastereoisomer of this unsaturated lactone rearranged on heating into a different isomer of a ten-membered cyclic diene. What sort of reaction is this, what kind of isomers are they, and how is the stereochemistry determined?



14. Suggest syntheses for this compound, explaining why you choose this particular approach.



Asymmetric synthesis

45

Connections

Building on:

- Carbonyl group reactions ch6, ch9, ch10, ch12, & ch14
- Controlling stereochemistry ch16, ch33, & ch34
- Electrophilic addition to alkenes ch20
- Aldol reactions ch27
- Diastereoselectivity ch33–ch34
- Cycloadditions ch35

Arriving at:

- Why making pure enantiomers matters
- Chirality derives from nature
- Resolution is the last resort
- The chiral pool provides starting materials
- Chiral auxiliaries are widely used with success
- Chiral reagents and catalysts may be even better
- Industrial asymmetric synthesis
- Two famous methods invented by Sharpless

Looking forward to:

- Main group chemistry ch46–ch47
- Organometallic chemistry ch48

Nature is asymmetrical—nature in the looking-glass

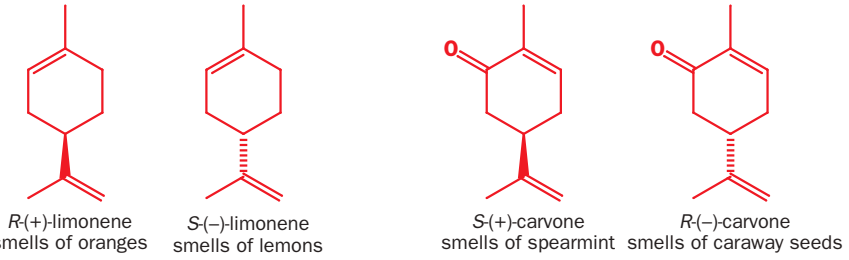
'How would you like to live in Looking-glass House, Kitty? I wonder if they'd give you milk in there? Perhaps looking glass milk isn't good to drink...' Lewis Carroll, *Through the looking-glass and what Alice found there*, Macmillan, 1872.

You are chiral, and so are Alice, Kitty, and all living organisms. You may think you look fairly symmetrical in a looking-glass, but as you read this book you are probably turning the pages with your right hand and processing the information with the left side of your brain. Some organisms are rather more obviously chiral: snails, for example, carry shells that could spiral to the left or to the right. Not only is nature chiral, but by and large it exists as just one enantiomer—though some snail shells spiral to the left, the vast majority of marine snail shells spiral to the right; all humans have their stomach on their left and their liver on their right; all honeysuckle climbs by spiralling to the left and all bindweed spirals to the right.

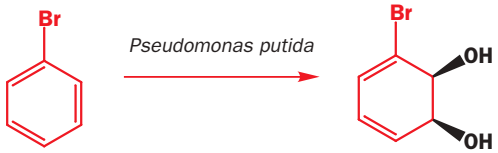
● 'L'univers est dissymmétrique', Louis Pasteur, *ca.* 1860

Nature has a left and a right, and it can tell the difference between them. You may think that human beings are sadly lacking in this respect, since as children we all had to learn, rather laboriously, which is which. Yet at an even earlier age, you could no doubt distinguish the smell of oranges from the smell of lemons, even though this is an achievement at least as remarkable as getting the right shoe on the right foot. The smells of orange and lemon differ in being the left- and right-handed versions of the same molecule, limonene. (*R*)-(+)-Limonene smells rounded and orangey; (*S*)-(–)-limonene is sharp and lemony. Similarly, spearmint and caraway seeds smell quite different, though again this pair of aromas differs only in being the enantiomeric forms of the ketone carvone.

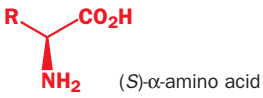
enantiomeric smells



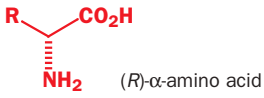
Even bacteria know their right from their left: *Pseudomonas putida* is a bacterium that can use aromatic hydrocarbons as a foodstuff, degrading them to diols. The diol produced from bromobenzene is formed as one enantiomer only.



How can this be? We said in Chapter 16 that enantiomers are chemically identical, so how is it that we can distinguish them with our noses and bacteria can produce them selectively? Well, the answer lies in a proviso to our assumption about the identity of enantiomers: they are identical *until they are placed in a chiral environment*. This concept will underlie all we say in this chapter about how to make single enantiomers in the laboratory. We take our lead from Nature: all life is chiral, so all living systems are chiral environments. Nature has chosen to make all its living structures from chiral molecules (amino acids, sugars), and has selected a single enantiomeric form of each. Every amino acid in your body has the *S* and not the *R* configuration, and from this fact, along with the uniform chirality of natural sugars, derives the larger scale chirality of all living structures from the DNA double helix to a blue whale's internal architecture. The answer to Alice's question is most certainly *no*—her kitten will be able to degrade the achiral fats in the milk quite easily, but the proteins (which will be made of *S*-amino acids) and L-lactose will be quite indigestible.



(*S*)-α-amino acid



(*R*)-α-amino acid

For a perfumer or flavour and fragrance manufacturer, the distinction between enantiomers of the same molecule is clearly of great importance. Nonetheless, we could all get by with caraway-flavoured toothpaste. Yet when it comes to drug molecules, making the right enantiomer can be a matter of life and death. Parkinson's disease sufferers are treated with the non-proteinogenic amino acid dopa (3-(3,4-dihydroxyphenyl)alanine; mentioned in Chapter 51). Dopa is chiral, and only (*S*)-dopa (known as L-dopa) is effective in restoring nerve function. (*R*)-dopa is not only ineffective; it is, in fact, quite toxic, so the drug must be marketed as a single enantiomer. We will look at how L-dopa is made industrially later in the chapter.

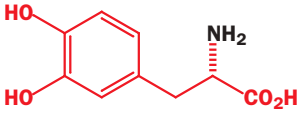
The amphetamine analogue fenfluramine, whose synthesis you designed while you were reading Chapter 31, used to be marketed as an anorectic (appetite-suppressant)—it stimulates the production of the hormone serotonin and makes the body feel satisfied—until it became clear that some undesirable side-effects could be avoided by administering it solely as the (*S*)-enantiomer. Fenfluramine 'relaunched' as the enantiomerically pure dexfenfluramine, and was reputedly 'a turning point for your overweight patients'—was available in the USA as a component of the 'slimming pill' Redux.

▶ Some bacteria make their cell walls from 'unnatural' *R*-amino acids to make them unassailable by the (*S*-amino-acid-derived) enzymes used by higher organisms to hydrolyse peptides.

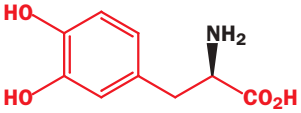
▶ You might, of course, retort that, in going through the looking-glass, perhaps Alice's kitten has undergone a universal inversion of configuration so that her proteins are all made of *R*-amino acids. Who can tell?

■ That is, dopa is not one of the 20 odd amino acids found in proteins; see Chapter 49.

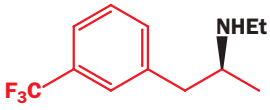
▶ There is no clear relationship between molecular chirality and the chirality of life forms. Right- and left-handed people are made from amino acids and sugars of the same handedness and the rare left-hand-spiralling snails have the same molecular chirality as their more common right-hand-spiralling relatives.



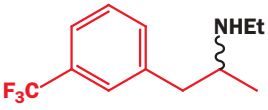
L-dopa
marketed as a single enantiomer



D-dopa
toxic

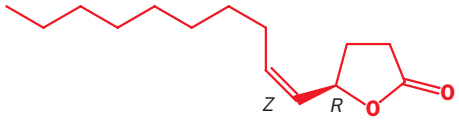


dexfenfluramine is an appetite suppressant



racemic fenfluramine has undesirable side-effects

It is not only drugs that have to be manufactured enantiomerically pure. This simple lactone is the pheromone released by Japanese beetles (*Popilia japonica*) as a means of communication. The beetles, whose larvae are serious crop pests, are attracted by the pheromone, and synthetic pheromone is marketed as 'Japonilure' to bait beetle traps. Provided the synthetic pheromone is the stereoisomer shown, with the *Z* double bond and the *R* configuration at the stereogenic centre, only 25 μg per trap catches thousands of beetles. You first met this compound in Chapter 32, where we pointed out that double bond stereocontrol was important since the *E*-isomer of the pheromone is virtually useless as a bait (it retains only about 10% of the activity). Even more important is control over the configuration at the chiral centre, because the *S*-enantiomer of the pheromone is not only inactive in attracting the beetles, but acts as a powerful inhibitor of the *R*-enantiomer—even 1% *S*-enantiomer in a sample of pheromone destroys the activity.



Japanese beetle pheromone

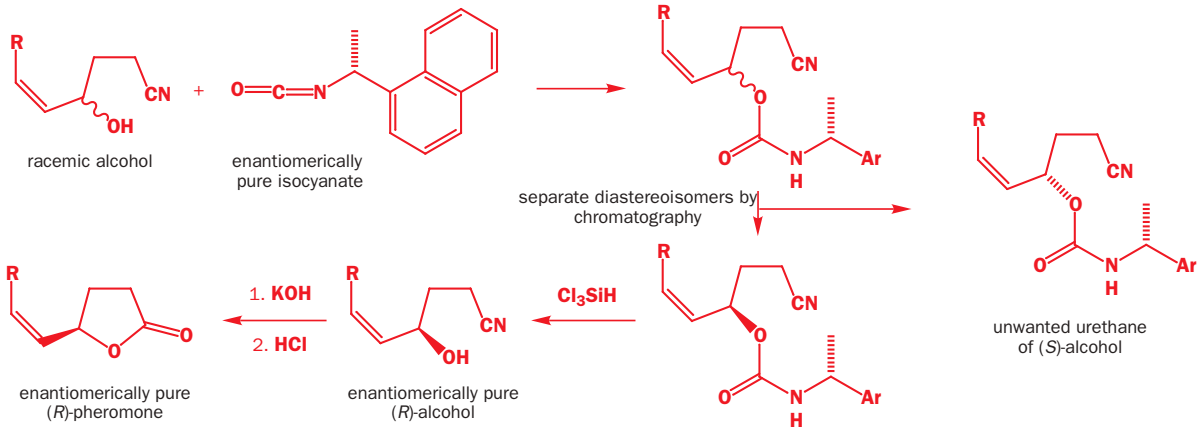
You can see why chemists need to be able to make compounds as single enantiomers. In Chapters 31–34 you looked at relative stereochemistry and how to control it; this chapter is about how to control absolute stereochemistry. In the last 20 years or so, this subject has occupied more organic chemists than probably any other, and we are now at a point where it is not only possible (and in fact essential, because of strict regulatory rules) to make many drug molecules as single enantiomers, but it is also even possible to make some molecules that are indigenous to nature more cheaply in the lab. At least 30% of the world's supply of menthol, for example, is not extracted from plants but is made in Japan using chemical techniques (which you will meet later in this chapter) that produce only a single enantiomer.

Resolution can be used to separate enantiomers

When we first introduced the concept of enantiomers and chirality in Chapter 16, we stressed that any imbalance in enantiomers always derives ultimately from nature. A laboratory synthesis, unless it involves an enantiomerically pure starting material or reagent, will always give a mixture of enantiomers. Here is just such a synthesis of the Japanese beetle pheromone you have just met. You can see the *Z*-selective Lindlar reduction in use—only one geometrical isomer of the double bond is formed—but, of course, the product is necessarily racemic and therefore useless as beetle bait, because in the original addition of the lithiated alkyne to the aldehyde there can be no control over stereochemistry. If all the starting materials and reagents are achiral, the product must be racemic.

racemic pheromone

In Chapter 16 we introduced you to resolution as a means of separating enantiomers, so if we want just the (*R*) compound, we could try that. Resolving the pheromone itself is not straightforward as there are no convenient functional groups to attach a resolving agent to. But the precursor alcohol can be resolved—William Pirkle did this by reacting the racemic alcohol with an enantiomerically pure isocyanate to make a mixture of the two diastereoisomeric amides which he then separated by chromatography. The resolving agent was removed from one of the diastereoisomers to give a single enantiomer of the alcohol, which could be cyclized to the natural (*R*)-pheromone using base and then acid.



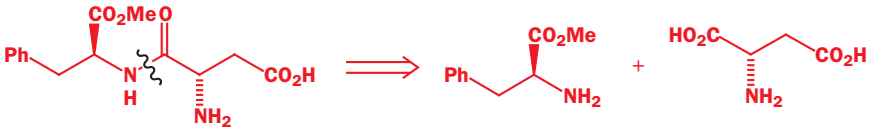
This is not, however, the method used to make Japanese beetle pheromone industrially. Resolution, as you have probably realized, is highly wasteful—if you want just one enantiomer, the other ends up being thrown away. In industrial synthesis, this is not an option unless recycling is possible, since chemical plants cannot afford the expense of disposing of such quantities of high-quality waste. So we need alternative methods of making single enantiomers.

▶ Later in this chapter, you will see an example of resolution of a compound (BINAP) for which there is a demand for *both* enantiomers as components of chiral catalysts. Resolution is the best option there.

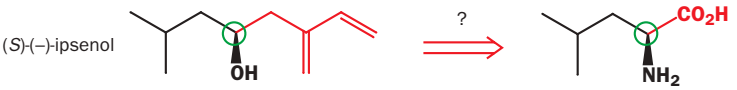
The chiral pool—Nature's 'ready-made' chiral centres

A more economical way of making compounds as single enantiomers is to manufacture them using an enantiomerically pure natural product as a *starting material*, rather than just using one as a resolving agent. This method is known as the **chiral pool strategy**, and relies on finding a suitable enantiomerically pure natural product—a member of the chiral pool—that can easily be transformed into the target molecule. The **chiral pool** is that collection of cheap, readily available pure natural products, usually amino acids or sugars, from which pieces containing the required chiral centres can be taken and incorporated into the product.

Sometimes the natural products that are needed are immediately obvious from the structure of the target molecule. An apparently trivial example is the artificial sweetener aspartame (marketed as Nutrasweet), which is a dipeptide. Clearly, an asymmetric synthesis of this compound will start with the two members of the chiral pool, the constituent (natural) (*S*)-amino acids, aspartic acid and phenylalanine. In fact, because phenylalanine is relatively expensive for an amino acid, significant quantities of aspartame derive from synthetic (*S*)-phenylalanine made by one of the methods discussed later in the chapter.



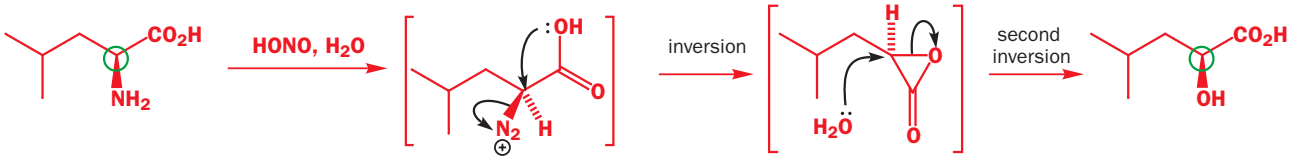
Most asymmetric syntheses require rather more than one or two steps from chiral pool constituents. Male bark beetles of the genus *Ips* produce a pheromone that is a mixture of several enantiomerically pure compounds. One is a simple diene alcohol (*S*)-(–)-ipsenol. Japanese chemists in the 1970s noted the similarity of part of the structure of ipsenol (in black) to the widely available amino acid (*S*)-leucine and decided to exploit this in a chiral pool synthesis, using the stereogenic centre (green ring) of leucine to provide the stereogenic centre of ipsenol.



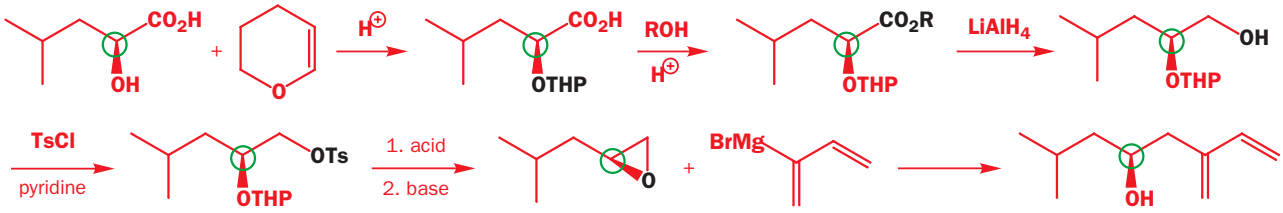
■ Participation was discussed in Chapters 37 and 41. You will see another example of conversion of NH_2 to OH with retention shortly. This is a useful reaction for converting amino acids to more versatile hydroxy-acids.

The amino group needs to be converted to a hydroxyl group with retention of configuration: diazotization followed by hydrolysis does just this because of neighbouring group participation from the carboxylic acid.

diazotization–hydrolysis of amino acids to give hydroxy-acids proceeds with overall retention

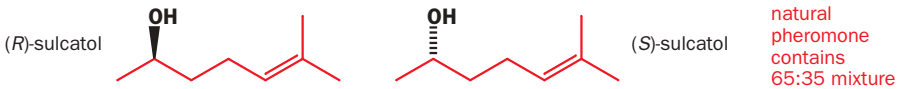


The alcohol was protected as the THP derivative (Chapter 24). Reduction of the acid, via the ester, then allowed introduction of the tosyl leaving group, which was displaced to make an epoxide. The epoxide reacted with a Grignard reagent carrying the diene portion of the target molecule.

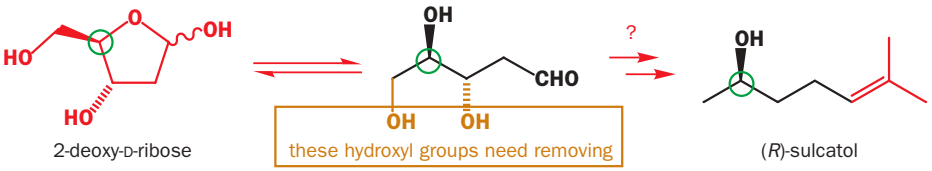


(*S*)-(–)-ipsenol

Another insect pheromone synthesis illustrates one of the drawbacks of chiral pool approaches. The ambrosia beetle aggregation pheromone is called sulcatol and is a simple secondary alcohol. This pheromone poses a rather unusual synthetic problem: the beetles produce it as a 65:35 mixture of enantiomers so, in order to mimic the pheromone's effect, the chemist has to synthesize both enantiomers separately and mix them together in the right proportion.

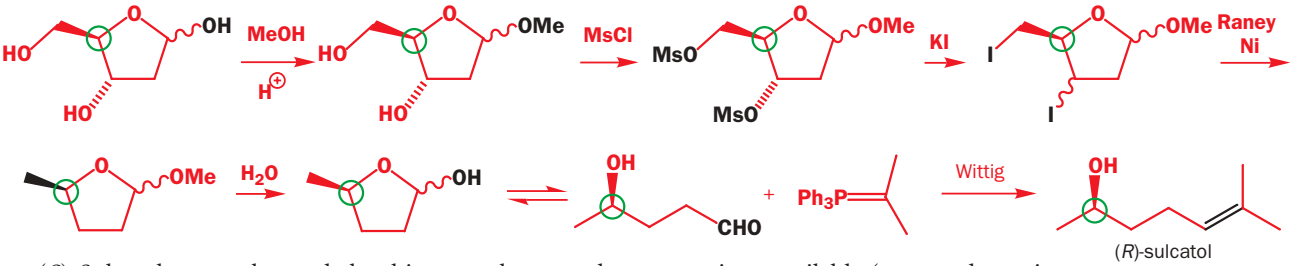


One approach to the (*R*)-enantiomer employs the sugar found in DNA, 2-deoxy-D-ribose, as a source of chirality.



Only one (ringed with green again) of the two defined chiral centres in the sugar appears in the product so, after protecting the hemiacetal, the two free hydroxyl groups were removed by mesylation, substitution by iodide, and reduction. A simple olefination gave (*R*)-sulcatol. Sugars often need simplifying in this way, because only rarely are all their chiral centres (most have more than two!) needed in the final product.

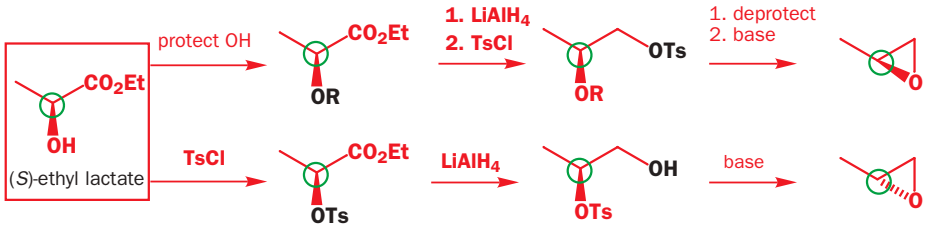
▶ The stereochemistry of the iodide formed from the secondary alcohol doesn't matter as it disappears in the next step.



(*S*)-Sulcatol cannot be made by this route, because the L-sugar is unavailable (even D-deoxyribose is quite expensive), so an alternative synthesis was needed that could be adapted to give either isomer. The solution is to go back to another hydroxy-acid, ethyl lactate, which is more widely available as its (*S*)-enantiomer, but which can be converted simply to either enantiomer of a key epoxide intermediate. From (*S*)-ethyl lactate, protection of the alcohol, reduction of the ester, and tosylation allows ring closure to one enantiomer of the epoxide; tosylation of the secondary hydroxyl group followed by reduction and ring closure gives the other enantiomer.

▶ Of course, here a resolution strategy would have been ideal!

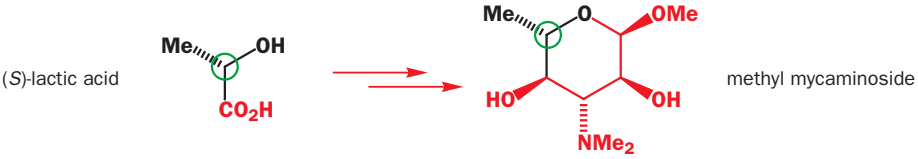
both enantiomers of propylene oxide can be made from (*S*)-ethyl lactate



For this reason, the two enantiomers of propylene oxide are commonly used as 'chiral pool' starting materials. These epoxides react with the appropriate Grignard reagent to give either enantiomer of the sulcatol.

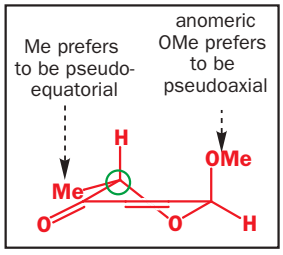
(*R*)- or (*S*)-propylene oxide (*R*)- or (*S*)-sulcatol

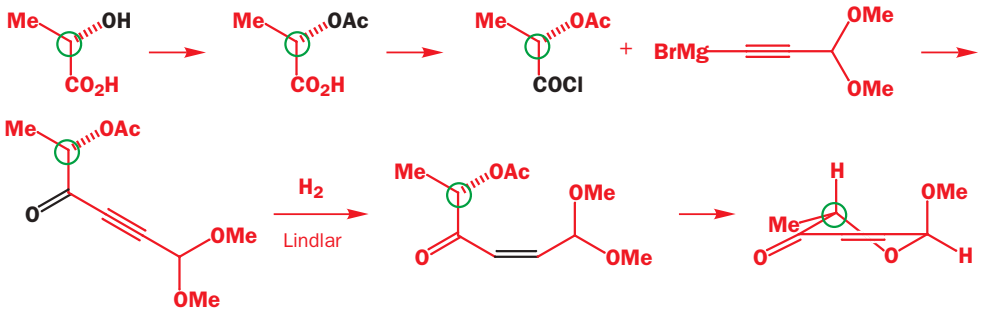
For targets with more than one stereogenic centre, only one need be borrowed from the chiral pool, provided diastereoselective reactions can be used to introduce the others with control over relative stereochemistry. Because the first chiral centre has defined absolute configuration, any diastereoselective reaction that controls the relative stereochemistry of a new chiral centre also defines its absolute configuration. In this synthesis of the rare amino sugar methyl mycamino- side, only one chiral centre comes directly from the chiral pool—the rest are introduced diastereoselectively.



(*S*)-lactic acid methyl mycaminoside

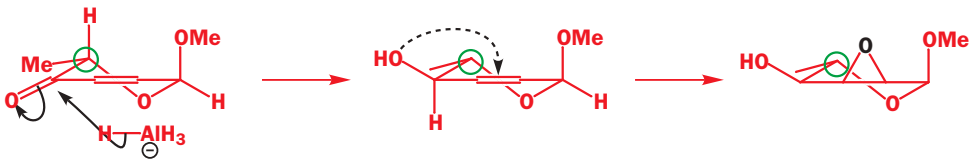
The ring was built up from acetylated (*S*)-lactic acid, and a cyclization step introduced the second chiral centre—the methyl group goes pseudoequatorial while the pseudoaxial position is preferred by the methoxy group because of the anomeric effect (Chapter 42).





■ In Chapter 18 the conformational factors governing reduction of cyclohexanones are discussed and the directing effects of OH groups in epoxidation are discussed in Chapters 33 and 34.

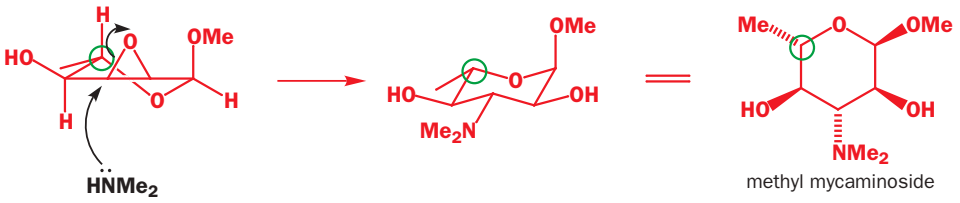
The third stereogenic centre was controlled by axial reduction of the ketone to give the equatorial alcohol, which then directed introduction of the fourth and fifth stereogenic centres by epoxidation.



axial attack leads to more stable equatorial alcohol

hydroxyl group directs epoxidation to top face by hydrogen bonding

Finally, the simple nucleophilic amine Me_2NH attacks the epoxide with inversion of configuration to give methyl mycaminoside. The conformational drawing shows that all substituents are equatorial except the MeO group, which prefers to be axial because of the anomeric effect.

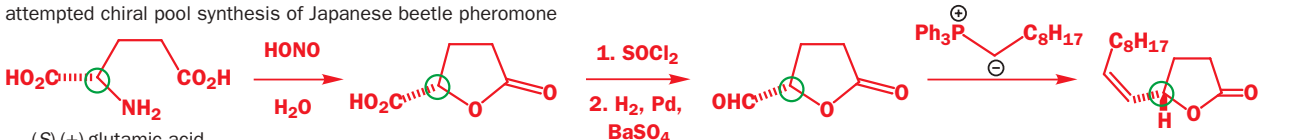


methyl mycaminoside

▶ Normally, axial attack occurs on cyclohexane epoxides as explained in Chapter 18 but the rule is not rigid as you can see here. Equatorial attack occurs here because the transition state already has much of the stability of the product. You should continue to assume axial attack unless told otherwise.

The trouble with chiral pool approaches is that the compound you make has to be pretty close in structure to one of the natural products that are readily available or the synthetic route becomes so tortuous that it's even more wasteful than resolution. The second major drawback is the lack of availability of both enantiomers of most natural products, especially useful starting materials like amino acids and sugars—we have just met this problem with the synthesis of sulcatol from deoxyribose. As a further example, we can return again to our Japanese beetles. Their pheromone can be made from glutamic acid by a short route. Unfortunately, when widely available (*S*)-(+)-glutamic acid is used, the product is the *enantiomer* of the active pheromone, which you will remember is a powerful inhibitor of the natural pheromone. Making the right enantiomer is not economical, because (*R*)-(–)-glutamic acid is about 40 times more expensive than (*S*)-(+)-glutamic acid.

attempted chiral pool synthesis of Japanese beetle pheromone



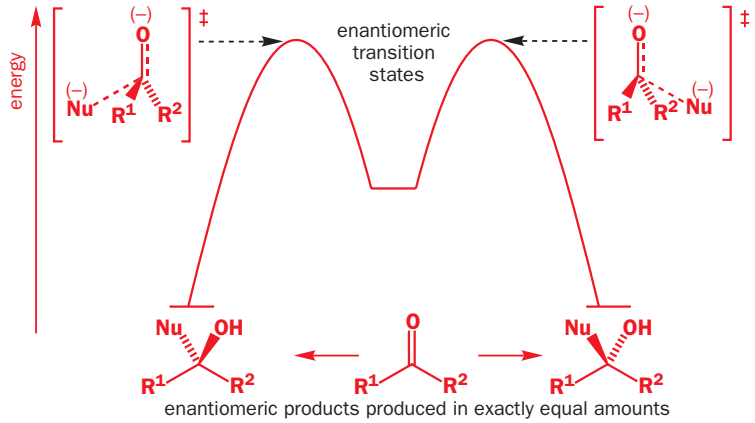
(*S*)-(+)-glutamic acid

the wrong enantiomer!
(plus 10–15% of its *E*-isomer)

Asymmetric synthesis

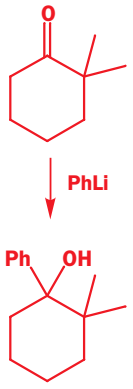
When we create a new stereogenic centre in a previously achiral molecule using achiral reagents (addition of CN^- to aldehydes was the example you met in Chapter 16), we get a racemic mixture because the transition states leading to the two enantiomers are themselves enantiomeric and therefore equal in energy.

nucleophilic attack on a ketone in an achiral environment.

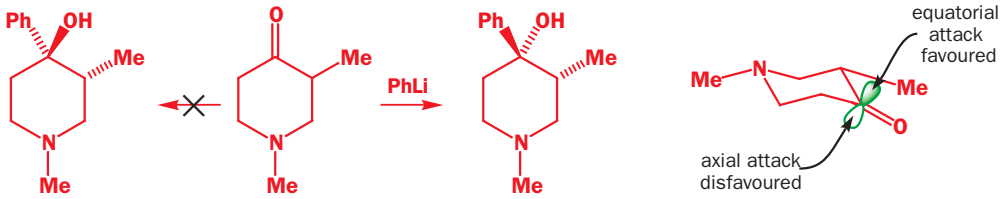


enantiomeric products produced in exactly equal amounts

example:

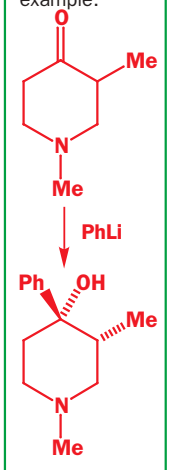


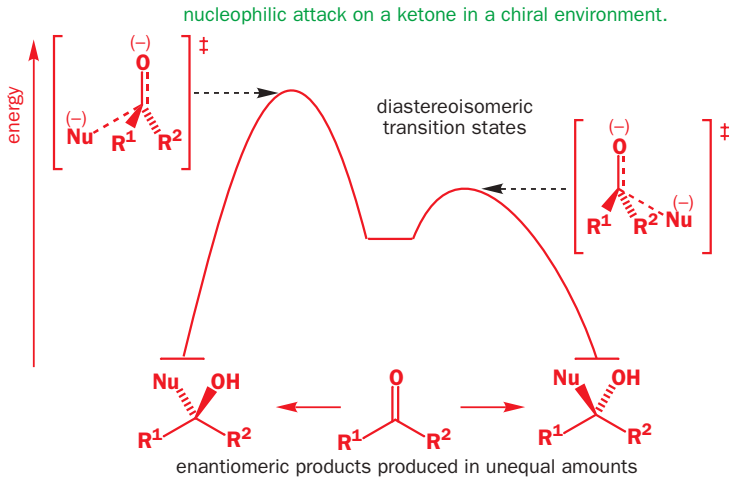
Diastereoselective synthesis, on the other hand, relies on making the transition states for reactions leading to different diastereoisomers as different in energy as possible and therefore favouring the formation of one diastereoisomer over another. You met this type of stereoselectivity in Chapter 33. Here is a simple example: PhLi adds to this ketone to give one diastereoisomer of the tertiary alcohol and not the other. Attack on one or other face of the ketone leads to diastereomeric transition states: this is perhaps most obvious when you realize that one is axial and one equatorial attack. An energy diagram for this type of reduction appears on the next page.



Now, let's go back to the principle of resolution and see how we can devise a way of improving upon it that doesn't require us to throw away 50% of our product. Resolution works because attaching an enantiomerically pure resolving agent to the racemic substrate distinguishes the substrate's two enantiomers as diastereoisomers (diastereoisomers are chemically different; enantiomers are not). Can we use this same idea to make two enantiomeric (and therefore equal in energy) *transition states* into diastereoisomeric ones (which will therefore be unequal in energy)? If we can, the lower-energy transition state will be favoured and we will get more of one enantiomer than the other.

example:



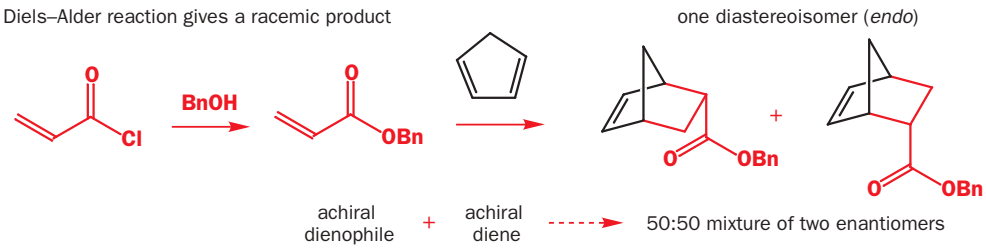


The answer is most definitely yes—what is needed is an enantiomerically pure molecule or part of a molecule that will be present during the reaction and will interact with the transition state of the reaction in such a way that it controls the formation of the new stereogenic centre. This molecule might be a reagent or a catalyst, or it might be covalently attached to the starting material. We will consider all of these possibilities, the last first, and you will see that they really are the most powerful and versatile ways of making enantiomerically pure compounds.

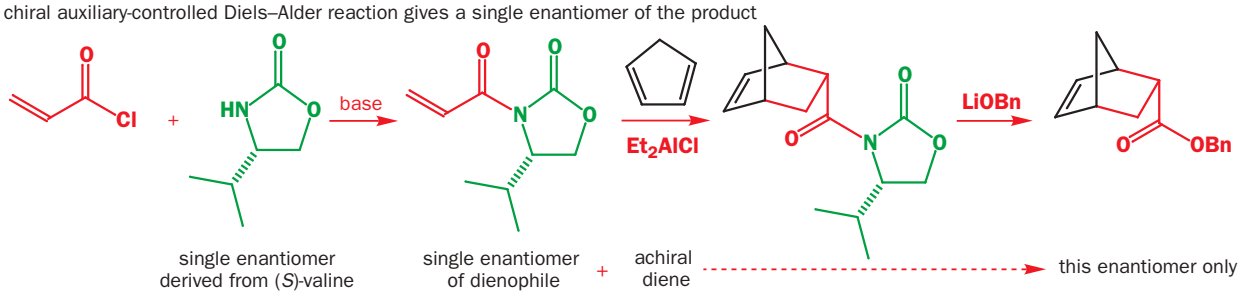
▶ 'Auxiliary' has but one 'l'.

Chiral auxiliaries

The product of a Diels–Alder reaction between cyclopentadiene and benzyl acrylate must necessarily be racemic as both reagents are achiral. Though only one *diastereoisomer*—the *endo* product—is formed, it must be formed as an exactly 50:50 mixture of *enantiomers*.

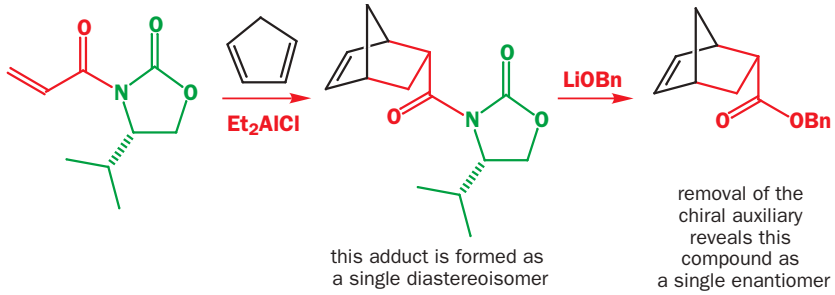


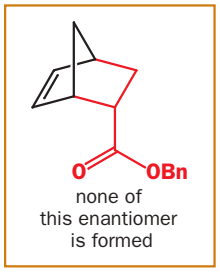
Now see what happens if we replace the achiral benzyl ester group with an amide derived from the natural amino acid valine (Chapter 49). The diastereoselectivity remains the same but the chiral environment created by the single enantiomer covalently bonded to the dienophile has a remarkable effect: only one enantiomer of the product is formed.



As far as stereoselectivity is concerned, the key step is the Diels–Alder reaction—in each case the diene (cyclopentadiene, shown in black) adds across the dienophile, an acrylic acid derivative. As you would expect from what we said in Chapter 35, both reactions are diastereoselective in that they generate mainly the *endo* product. In the first example, that is all there is to say: the product that is formed is necessarily racemic because all the starting materials in the reaction were achiral.

But, in the second example, a green **chiral auxiliary** has been attached to one of the starting materials. It contains another stereogenic centre and is enantiomerically pure—it was, in fact, made by a chiral pool strategy from the amino acid (*S*)–valine (see below). You can see that it has quite an effect on the reaction—the extra stereogenic centre means that there are now *two* possible diastereoisomeric *endo* products, but only one is formed.





The chiral auxiliary was enantiomerically pure—every molecule had the same configuration at its stereogenic centre. That centre was not involved in the Diels–Alder reaction, so all the products will similarly have the same configuration at the stereogenic centre in the green part of the molecule. So, if one diastereoisomer of the product is formed, all the stereogenic centres in that product must be of a single configuration; in other words the product is diastereoisomerically *and* enantiomerically pure. And when we do the final step of the sequence, to remove the chiral auxiliary, that enantiomeric purity remains, despite the fact that we have removed its source. Overall, by sequential attachment and removal of the auxiliary we have made the same product but as a single enantiomer.

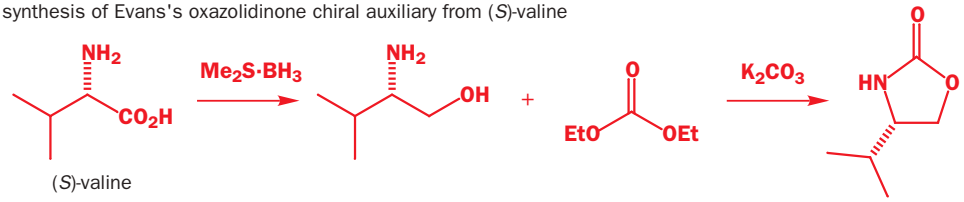
▶ You may note the inclusion of the Et_2AlCl Lewis acid catalyst in the second reaction. As we discussed in Chapter 35, the presence of a Lewis acid increases the rate of Diels–Alder reactions, and in this case is also vital for high stereoselectivity.

This is what we mean by a chiral auxiliary strategy

1. **An enantiomerically pure compound (usually derived from a simple natural product like an amino acid), called a chiral auxiliary, is attached to the starting material.**
2. **A diastereoselective reaction is carried out, which, because of the enantiomeric purity of the chiral auxiliary, gives only one enantiomer of the product.**
3. **The chiral auxiliary is removed by, for example, hydrolysis, leaving the product of the reaction as a single enantiomer. The best chiral auxiliaries (of which the example above is one) can be recycled, so although stoichiometric quantities are needed, there is no waste.**

We have introduced you to this chiral auxiliary before any other because it is more commonly used than any other. It is a member of the oxazolidinone (the name of the heterocyclic ring) family of auxiliaries developed by David Evans at Harvard University, and is easily and cheaply made from the amino acid (*S*)-valine. Not only is it cheaply made: it can also be recycled. The last step of the route above, transesterification with benzyl alcohol, regenerates the auxiliary ready for re-use.

synthesis of Evans's oxazolidinone chiral auxiliary from (*S*)-valine



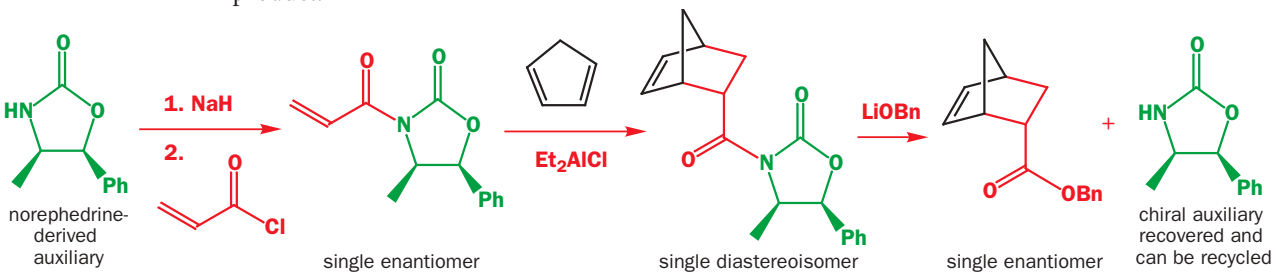
(*S*)-valine

The most versatile chiral auxiliaries should also be available as both enantiomers. Now, for the valine-derived one here, this is not the case—(*R*)-valine is quite expensive since it is not found in nature. However, by starting with the naturally occurring (and cheap) compound norephedrine, we can make an auxiliary that, although not enantiomeric with the one derived from (*S*)-valine, acts as though it were. Here is the synthesis of the auxiliary.

norephedrine

norephedrine-derived auxiliary

And here it is promoting the same asymmetric Diels–Alder reaction, but giving the enantiomeric product.



norephedrine-derived auxiliary

single enantiomer

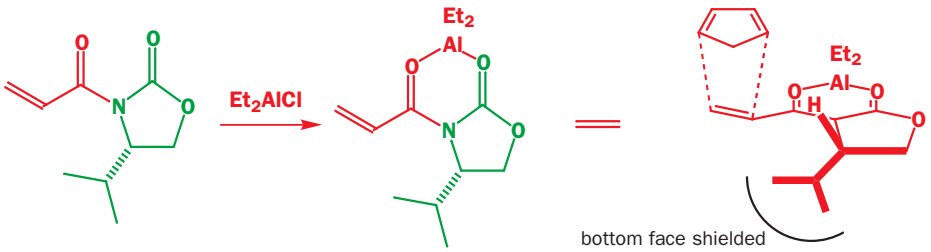
single diastereoisomer

single enantiomer

chiral auxiliary recovered and can be recycled

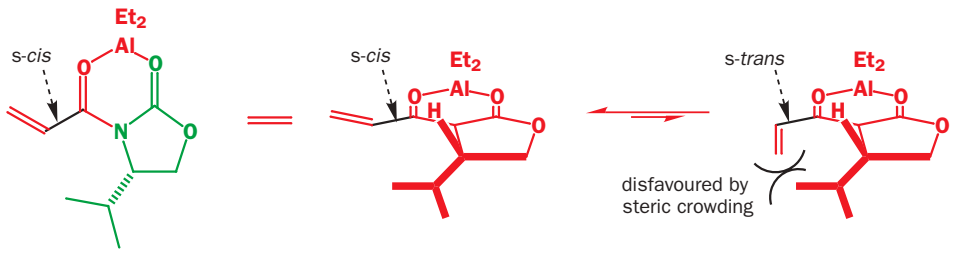
How do these auxiliaries fulfil their role? If we go back to the valine-derived auxiliary and draw the auxiliary-bearing dienophile coordinated with the Lewis acid you can clearly see that the isopropyl group shields the back face of the alkene from attack: when the cyclopentadiene moves in, it must approach from the front face (and remember it will align itself to gain maximum secondary orbital stabilization and therefore give the *endo* product).

cyclopentadiene must attack from top face



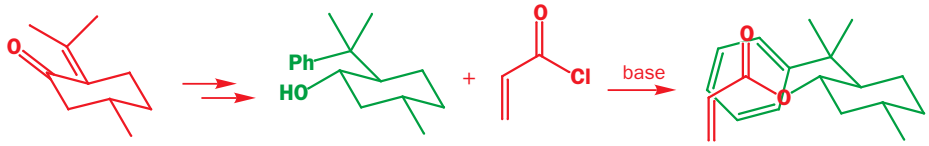
bottom face shielded

Note that the auxiliary also has the effect of fixing the conformation of the black single bond as s-*cis* (we introduced this nomenclature on p. 000). Attack on the top face of the s-*trans* compound would give the enantiomeric product.



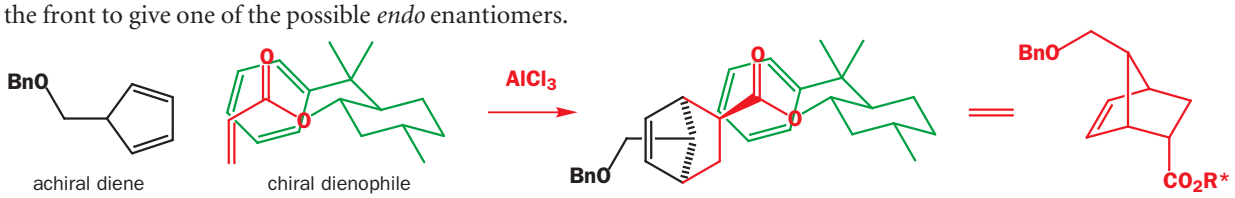
The auxiliary has succeeded in doing what we set out to do (p. 000)—it has made diastereoisomeric the transition states leading to enantiomeric products, the difference in energy arising because of steric crowding of one face of the alkene.

Lest you should imagine that all effective auxiliaries are oxazolidinones, here is a different one—8-phenylmenthol—used by Corey in enantioselective prostaglandin synthesis. 8-Phenylmenthol is made from the natural product pulegone (Chapter 51). Even in the starting material the role of the phenyl group is clearly to crowd one face of the dienophile.



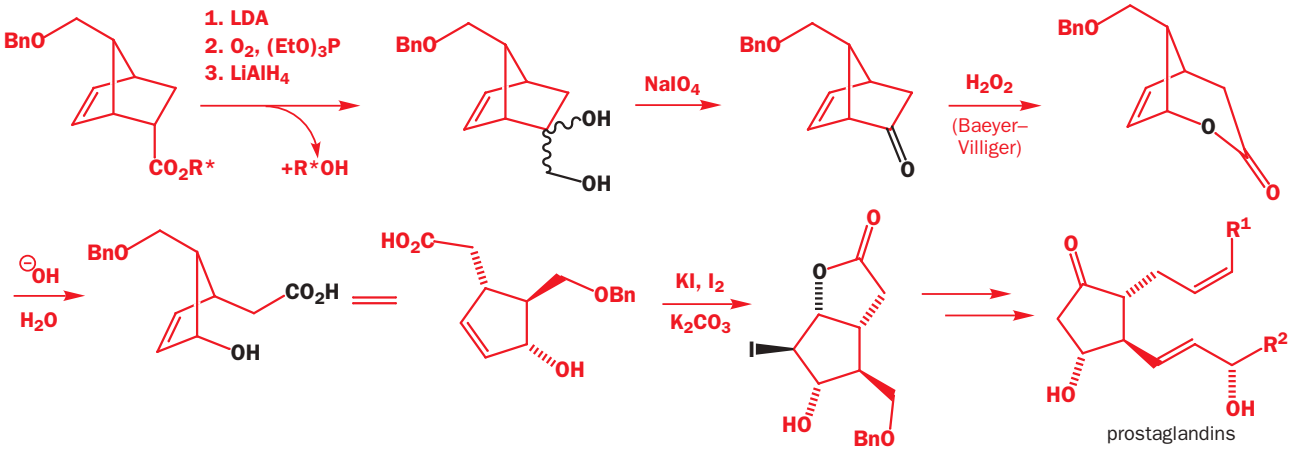
(*S*)-pulegone 8-phenylmenthol chiral dienophile

A Lewis acid ($AlCl_3$)-catalysed Diels–Alder reaction with a substituted, but still achiral, cyclopentadiene gives a single enantiomer of the adduct. The sense of asymmetry induced in the reaction is seen more clearly if we redraw the product with 'R*' to represent the chiral auxiliary. The phenyl group on the auxiliary shields the back of the dienophile (as drawn) so that the diene has to add from the front to give one of the possible *endo* enantiomers.



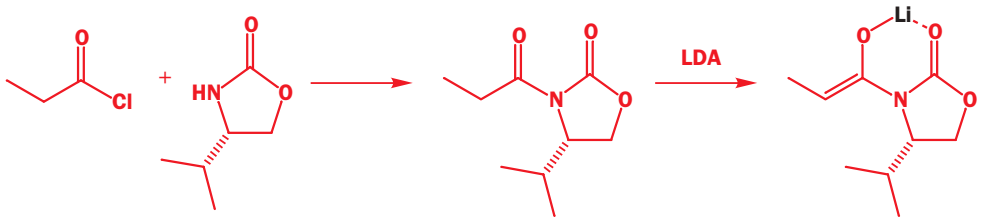
achiral diene chiral dienophile

Corey used the four chiral centres created in the reaction to provide the chiral centres around the cyclopentanone ring of the prostaglandins (a family of compounds implicated in inflammation; see Chapter 51). After hydroxylation of the ester's enolate, the auxiliary was removed, this time by reduction. Diol cleavage with periodate (mentioned at the end of Chapter 35) gave a ketone that underwent Baeyer–Villiger oxidation on the more substituted side to give a hydrolysable lactone. Iodolactonization gave a substituted cyclopentanone that Corey used as a starting material for several important prostaglandin syntheses.



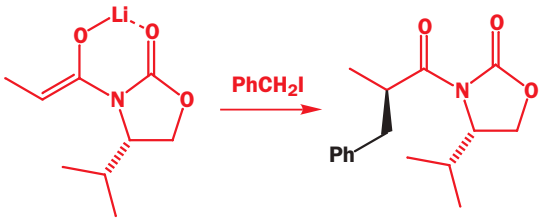
Alkylation of chiral enolates

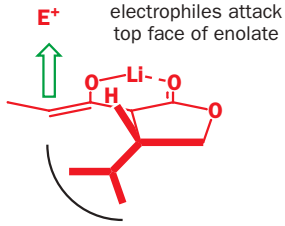
Chiral auxiliaries can be used in plenty of other reactions, and one of the most common types is the alkylation of enolates. Evans's oxazolidinone auxiliaries are particularly appropriate here because they are readily turned into enolizable carboxylic acid derivatives.



Treatment with base (usually LDA) at low temperature produces an enolate, and you can clearly see that the auxiliary has been designed to favour attack by electrophiles on only one face of that enolate. Notice too that the bulky auxiliary means that only the *Z*-enolate forms: alkylation of the *E*-enolate on the top face would give the diastereoisomeric product. Coordination of the lithium ion to the other carbonyl oxygen makes the whole structure rigid, fixing the isopropyl group where it can provide maximum hindrance to attack on the 'wrong' face.

Electrophile	Ratio of diastereoisomers
$PhCH_2I$	>99:1
allyl bromide	98:2
EtI	94:6



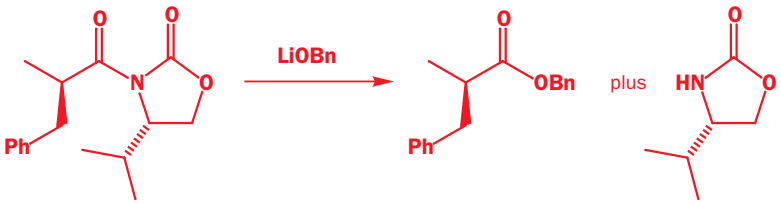


bottom face shielded by isopropyl group

The table in the margin shows the ratio of diastereoisomers produced by this reaction for a few alkylating agents. As you can see, none of these reactions is truly 100% diastereoselective and, indeed, only the best chiral auxiliaries (of which this is certainly one) give >98% of a single diastereoisomer. The problem with less than perfect diastereoselectivity is that, when the chiral auxiliary is removed, the final product is contaminated with some of the other enantiomer. A 98:2 ratio of diastereoisomers will result in a 98:2 ratio of enantiomers.

Enantiomeric excess

When talking about compounds that are neither racemic nor enantiomerically pure (usually called **enantiomerically enriched** or, occasionally, **scalemic**) chemists talk not about ratios of enantiomers but about **enantiomeric excess**. Enantiomeric excess (or **ee**) is defined as the excess of one enantiomer over the other, expressed as a percentage of the whole. So a 98:2 mixture of enantiomers consists of one enantiomer in 96% excess over the other, and we call it an enantiomerically enriched mixture with 96% ee. Why not just say that we have 98% of one enantiomer? Enantiomers are not like other isomers because they are simply mirror images. The 2% of the wrong enantiomer makes a racemate of 2% of the right isomer so the mixture contains 4% racemate and 96% of one enantiomer. 96% ee.



98:2 mixture of diastereoisomers

98:2 mixture of enantiomers
96% enantiomeric excess

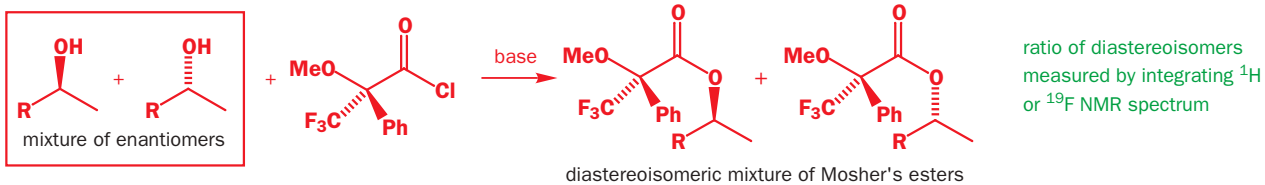
We will see shortly how we can make further use of the chiral auxiliary to increase the ee of the reaction products. But, first, we should consider how to measure ee. One way is simply to measure the angle through which the sample rotates plane-polarized light. The angle of rotation is proportional to the enantiomeric excess of the sample (see the Box). The problem with this method is that to measure an actual value for ee you need to know what rotation a sample of 100% ee gives, and that is not always possible. Also, polarimeter measurements are notoriously unreliable—they depend on temperature, solvent, and concentration, and are subject to massive error due to small amounts of highly optically active impurities.

Optical rotation should be proportional to enantiomeric excess

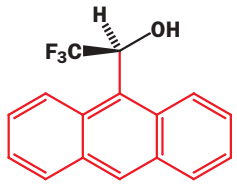
Imagine you have a sample, A, of an enantiomerically pure compound—a natural product perhaps—and, using a polarimeter, you find that it has an $[\alpha]_D$ of +10.0. Another sample, B, of the same compound, which you know to be *chemically* pure (perhaps it is a synthetic sample), shows an $[\alpha]_D$ of +8.0. What is its enantiomeric excess? Well, you would have got the same value of 8.0 for the $[\alpha]_D$ of B if you had mixed 80% of your enantiomerically pure sample A with 20% of a racemic (or achiral) compound with no optical rotation. Since you know that sample B is chemically pure, and is the same compound as A, it must therefore indeed consist of 80% enantiomerically pure material plus 20% racemic material, or 80% of one enantiomer plus 20% of a 1:1 mixture of the two enantiomers—which is the same as 90% of one enantiomer and 10% of the other, or 80% enantiomeric excess. Optical rotations can give a guide to enantiomeric excess—sometimes called **optical purity** in this context—but slight impurities of compounds with large rotations can distort the result and there are some examples where the linear relationship between ee and optical rotation fails because of what is known as the Horeau effect. You can read more about this in Eliel and Wilen, *Stereochemistry of organic compounds*, Wiley, 1994.

Modern chemists usually use either chromatography or spectroscopy to tell the difference between enantiomers. You may protest that we have told you that this is impossible—enantiomers are chemically identical and have identical NMR spectra, so how can chromatography or spectroscopy tell them apart? Well, again, they are identical unless they are in a chiral environment (the principle on which resolution relies). We introduced HPLC on a chiral stationary phase as a way of separating enantiomers preparatively in Chapter 16. The same method can be used analytically—less than a milligram of chiral compound can be passed down a narrow column containing chirally modified silica. The two enantiomers are separated and the quantity of each can be measured (usually by UV absorption or by refractive index changes) and an ee derived. Gas chromatography can be used in the same way—the columns are packed with a chiral stationary phase such as this isoleucine derivative.

Separating enantiomers spectroscopically relies again on putting them into a chiral environment. One way of doing this, if the compound is, say, an alcohol or an amine, is to make a derivative (an ester or an amide) with an enantiomerically pure acyl chloride. The one most commonly used is known as Mosher's acyl chloride, after its inventor Harry Mosher, though there are many others. The two enantiomers of the alcohol or amine now become diastereoisomers, and give different peaks in the NMR spectrum—the integrals can be used to determine ee and, although the ^{1}H NMR of such a mixture of diastereoisomers may become quite cluttered because it is a mixture, the presence of the CF_3 group means that the ratio can alternatively be measured by integrating the two singlets in the very simple ^{19}F NMR spectrum.



Insert Graphic Spectrum 45.1
Diagram of spectrum? PDW?



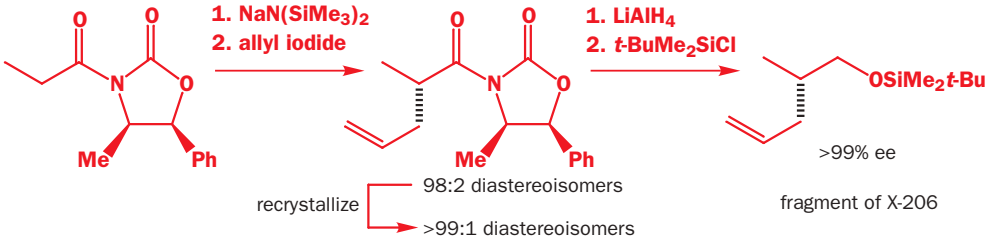
(*S*)-(+)-TFAE

Another powerful method of discriminating between enantiomers is to add an enantiomerically pure compound to the NMR sample that does not react with the compound under investigation but simply forms a complex with it. The complexes formed from enantiomers are diastereoisomeric and therefore have different chemical shifts and, by integrating the NMR signals, the ratio of enantiomers can be determined. In the past, lanthanide salts of enantiomerically pure weak acids (called **chiral shift reagents**), which formed Lewis acid–base complexes with oxygen atoms in the compound under investigation, were used. More common nowadays is this alcohol, 2,2,2-trifluoro-1-(9-anthryl)ethanol, or TFAE, which can both hydrogen-bond to and form π-stacking complexes with many compounds, and often splits enantiomeric resonances very cleanly. Again the ^{19}F or ^{1}H NMR spectrum can be used.

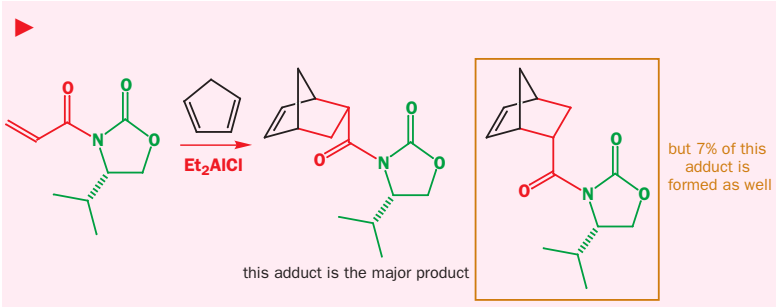
Insert Graphic Spectrum 45.2
Diagram of spectrum? PDW?

Let's go back to chiral auxiliaries. We said that, although we want to get maximum levels of stereoselectivity in our chiral-auxiliary-controlled reaction, we may still have 1 or 2% of a minor diastereoisomer, which, once we have removed our chiral auxiliary, will compromise the ee of our final product. It is at this point that we can use a trick that essentially employs the chiral auxiliary in a secondary role as a resolving agent. Provided the products are crystalline, it will usually be possible to recrystallize our 98:2 mixture of diastereoisomers to give essentially a single diastereoisomer, rather like carrying out a resolution with an enormous head start. Once this has been done, the chiral auxiliary can be removed and the product may be very close to 100% ee. Of course, the recrystallization sacrifices a few percentage points of yield, but these are invariably much less valuable than the few percentage points of ee gained! Here is an example from the work of Evans himself. During his synthesis of the complex antibiotic X-206 he needed large quantities of the small molecule below. He decided to make it by a chiral-auxiliary-controlled alkylation, followed by reduction to give the alcohol. The auxiliary needed is the one derived from norephedrine, and the alkylation with allyl iodide gives a 98:2 mixture of diastereoisomers. However, recrystallization converted this into an 83% yield

of a single diastereoisomer in >99% purity, giving material of essentially 100% ee after removal of the auxiliary.



This is one big bonus of using a chiral auxiliary—it's much easier to purify diastereoisomers than enantiomers and a chiral auxiliary reaction necessarily produces diastereoisomeric products.



At this point we should come clean about the asymmetric Diels–Alder reaction we introduced earlier. In fact, the diastereoisomer in the brown frame is formed in a 7% yield, with the major isomer accounting for 93%. But just one recrystallization gave >99% diastereoisomerically pure material in 81% yield.

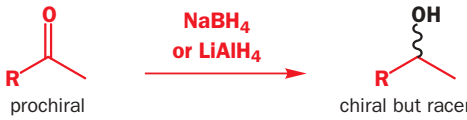
But there are, of course, disadvantages. Chiral auxiliaries must be attached to the compound under construction, and after they have done their job they must be removed. The best auxiliaries can be recycled, but even then there are still at least two 'unproductive' steps in the synthesis. We may have given the impression that successful asymmetric synthesis is made possible by joining any chiral compound to the substrate. This is very far from the truth. Discovering successful chiral auxiliaries requires painstaking research and most potential chiral auxiliaries give low ees in practice. More efficient may be chiral reagents, or, best of all, chiral catalysts, and it is to these that we turn next.

Chiral reagents and chiral catalysts

If we want to create a new chiral centre in a molecule, our starting material must have **prochirality**—the ability to become chiral in one simple transformation. The most common prochiral units that give rise to new chiral centres are the trigonal carbon atoms of alkenes and carbonyl groups, which become tetrahedral by addition reactions. In all of the examples you saw in the last section, a prochiral alkene (we can count enolates as alkenes for this purpose) reacted selectively on one face because of the influence of the chiral auxiliary, which made the faces of the alkene diastereotopic.

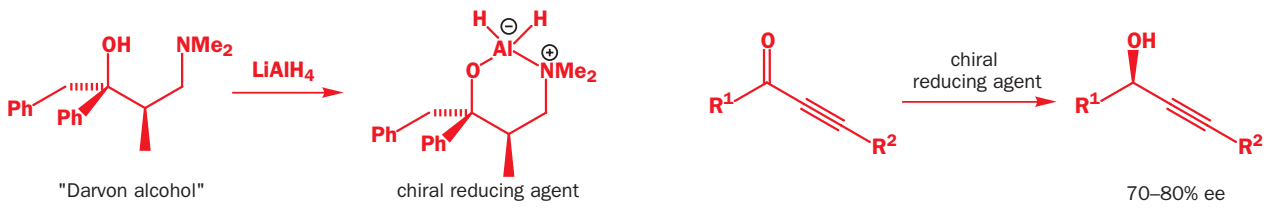
Go back to Chapters 32–34 if you need reminding about the terms prochiral, enantiotopic, and diastereotopic.

One of the simplest transformations you could imagine of a prochiral unit into a chiral one is the reduction of a ketone. Although chiral auxiliary strategies have been used to make this type of reaction asymmetric, you will appreciate that, conceptually, the simplest way of getting the product as a single enantiomer would be to use a chiral reducing agent—in other words, to attach the chiral influence not to the substrate (as we did with chiral auxiliaries) but to the reagent.

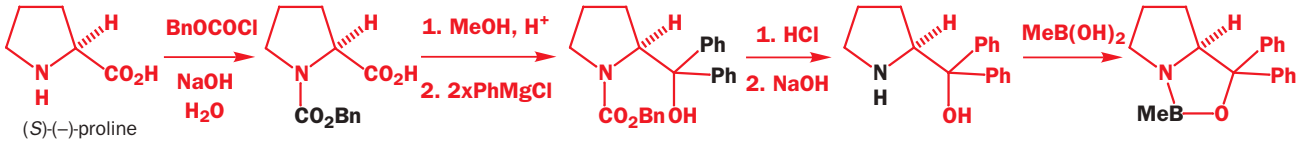


One of the earliest attempts to do this used $LiAlH_4$ as the reducing agent and made it chiral by attaching 'Darvon alcohol' to it. Unfortunately, this reagent is not very effective—successful substrates are confined to acetylenic alcohols, and even then the products are formed with a maximum of about 80% ee.

Esters of 'Darvon alcohol' and its enantiomer are the drugs Darvon and Novrad (see p. 000)—hence the ready availability of this compound.



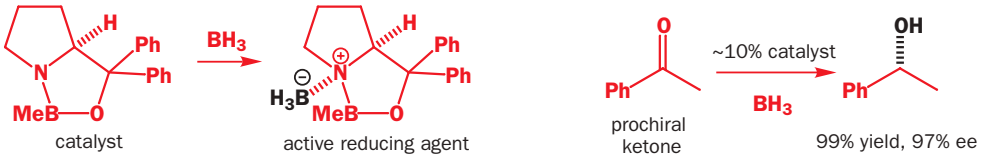
More effective is the chiral borohydride analogue developed by Corey, Bakshi, and Shibita. It is based upon a stable boron heterocycle made from an amino alcohol derived from proline, and is known as the **CBS reagent** after its developers.



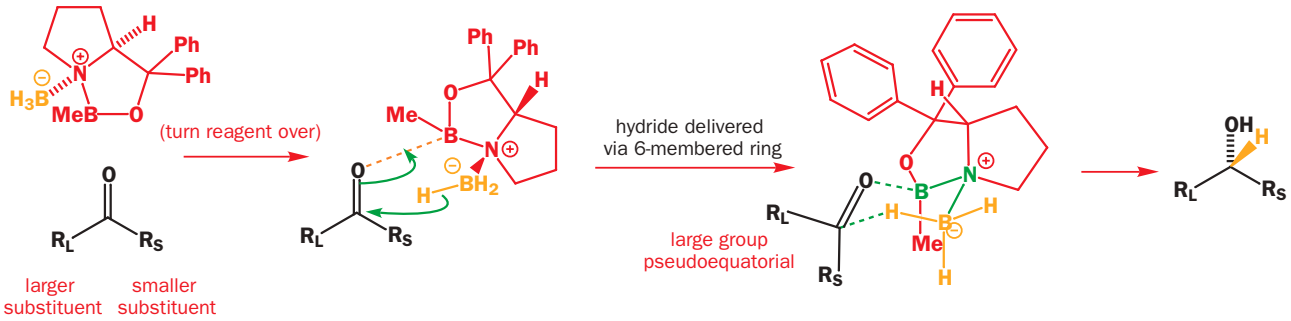
▶Catalysts not reagents

The fact that the reactions are catalytic in the heterocycle means that relatively little is needed and it can be recovered at the end of the reaction. Later in the chapter you will see catalytic reactions that use 1000 times less catalyst than this one and, indeed, none of the reactions we will mention in the rest of this chapter will use chiral reagents—only chiral catalysts. Note the distinction from chiral auxiliaries here: although auxiliaries are recoverable, they always have to be used in stoichiometric quantities, and recovery is usually a separate step.

The active reducing agent is made by complexing the heterocycle with borane. Only catalytic amounts (usually about 10%) of the boron heterocycle are needed because borane is sufficiently reactive to reduce ketones only when complexed with the nitrogen atom. The rest of the borane just waits until a molecule of catalyst becomes free.



CBS reductions are best when the ketone's two substituents are well-differentiated sterically—just as Ph and Me are in the example above. Only when the ketone is complexed with the 'other' boron atom (in the ring) is it electrophilic enough to be reduced by the weak hydride source. The hydride is delivered via a six-membered cyclic transition state, with the enantioselectivity arising from preference of the larger of the ketone's two substituents (R_L) for the pseudoequatorial position on this ring.



The CBS reagent is one of the best asymmetric reducing agents invented by chemists. Yet Nature does asymmetric reductions all the time—and gets 100% ee every time too. Nature uses enzymes as chiral catalysts, and chemists have not been slow to subvert these natural systems to their own ends. The problem with using enzymes is that they are designed to fit into a single biochemical pathway and are often quite substrate-specific, and so are not useful as a general chemical method. However, this can be overcome by using conveniently packaged multienzyme systems, living cells. Yeast is particularly good at reducing ketones, and the best enantioselectivies are obtained when the ketone carries a β-ester group. The reaction is done by stirring the ketone with an aqueous suspension of live yeast, which must be fed with plenty of sugar.

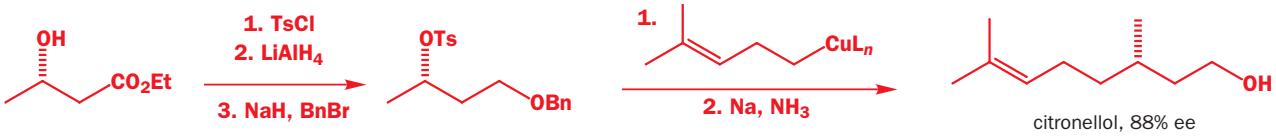
■

Reductions with Nature's CBS reagent—NADH—are discussed in Chapter 51.

These reactions are quite messy, and are best done on a large scale! Notice how the selectivity of baker's yeast is the reverse of that of the CBS reagent with respect to the large and small ketone substituents. This is most useful, since (*R*)-proline is expensive, and an enantiomeric yeast cell would be a rarity indeed.

▶ In fact, the enantiomer of the CBS reagent can be made by a resolution strategy.

An important application of this baker's yeast reduction is in the synthesis of citronellol. After reduction and protection of the ester, S_N2 substitution of the secondary tosylate group could be achieved with inversion using a copper nucleophile. The 88% ee obtained here is better than that of many natural samples of citronellol: in common with many other terpenes, citronellol extracted from plants varies greatly in enantiomeric purity. It is quite a compliment to the humble yeast that, with a bit of help from Professor Mori's research group, it can outdo most of the more sophisticated members of the plant kingdom.



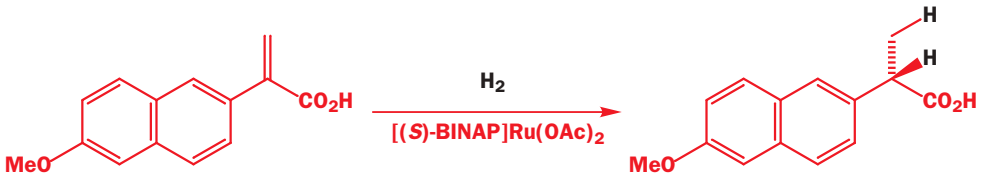
substitution with inversion

citronellol, 88% ee

Asymmetric hydrogenation

Probably the best-studied way of carrying out enantioselective reduction is to hydrogenate in the presence of a chiral catalyst. You would not normally choose catalytic hydrogenation for reducing a carbonyl group to an alcohol and, indeed, carbonyl reductions using hydrogenation with a chiral catalyst are not usually very enantioselective. Much better are hydrogenations of double bonds, particularly those with nearby heteratoms (OH, NHR) that can coordinate to the metal.

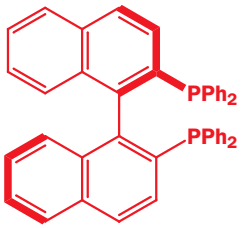
Here is a simple example: it is, in fact, an asymmetric synthesis of the analgesic drug naproxen. First, look at the reaction—we'll consider the catalyst in a moment.

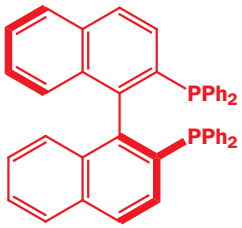


(*S*)-naproxen

The principle is quite simple—the catalyst selects a single enantiotopic face of the double bond and adds hydrogen across it. Exactly how it does this need not concern you, but we do need to go into more detail about the structure of the catalyst, which consists of a metal atom (Ru) and a ligand, called BINAP.

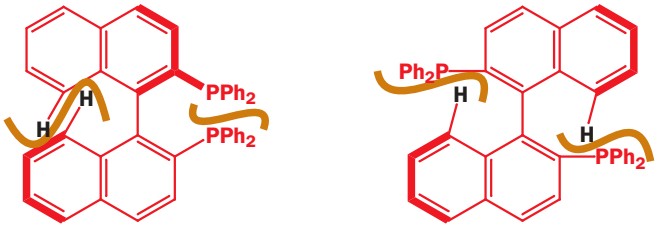
(*R*)-BINAP





(*S*)-BINAP

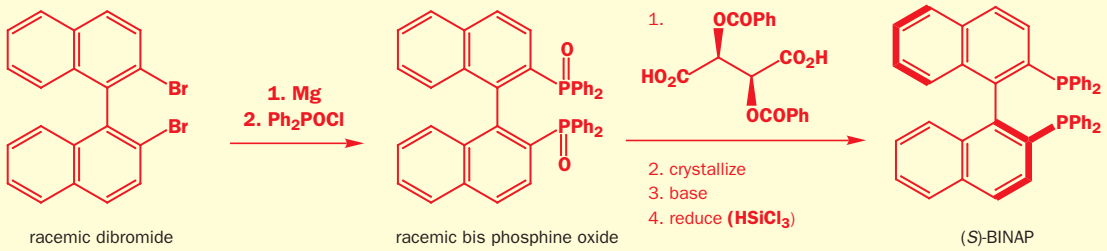
In common with many other ligands for asymmetric hydrogenation, BINAP is a chelating diphosphine: the metal sits between the two phosphorus atoms firmly anchored in a chiral environment. The chirality here is of an unusual sort, since BINAP has no chiral centres. Instead it has **axial chirality** by virtue of restricted rotation about the bond joining the two naphthalene ring systems. In order for the two enantiomers of BINAP to interconvert, the PPh_2 group would have to force its way either past the other PPh_2 group or round the black hydrogen (see next page). Both pathways are too strained for racemization to occur.



BINAP is not derived from a natural product, and has to be synthesized in the laboratory and resolved.

Resolution of BINAP

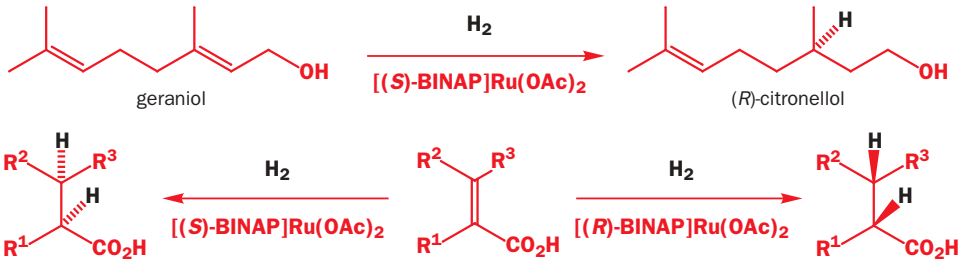
The scheme shows one method by which BINAP may be made—the resolution step is unusual because it relies on formation of a molecular complex, not a salt. It is the phosphine oxide that is resolved, and then reduced to the phosphine with trichlorosilane.



racemic dibromide — racemic bis phosphine oxide — (*S*)-BINAP

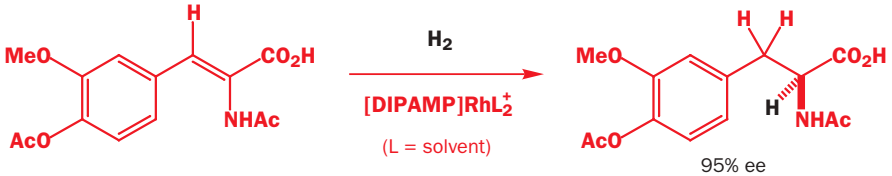
This makes it relatively expensive, but the expense is offset by the economy of catalyst required in such reactions. Whereas about 10 mol% catalyst is needed for CBS reductions, many hydrogenations of this type give high enantiomeric excesses with only 0.0002 mol% BINAP–ruthenium(II) catalyst! Because such minuscule quantities of catalyst are needed, enantioselective hydrogenations are more widely used by industry than any other asymmetric method. The other advantage of the resolution is, of course, that either enantiomer is equally available.

BINAP–ruthenium(II) is particularly good at catalysing the hydrogenation of allylic alcohols, and of α,β-unsaturated carboxylic acids to give acids bearing α stereogenic centres (like naproxen above).



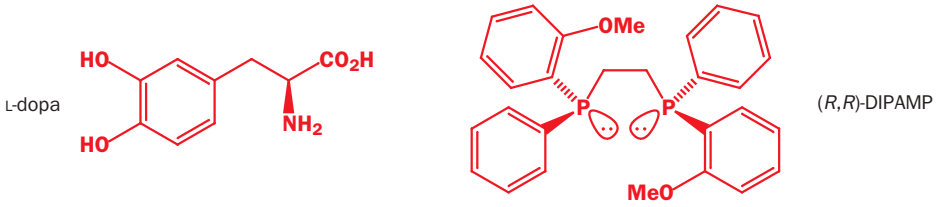
geraniol — (*R*)-citronellol

If the double bond also bears an amino group, the products of these reactions are α amino acids, and in these cases there is another alternative that works even better, a catalyst based on rhodium. Here is one very important synthesis of an unnatural amino acid using a rhodium catalyst. Again, look first at the reaction and then we will discuss the catalyst.

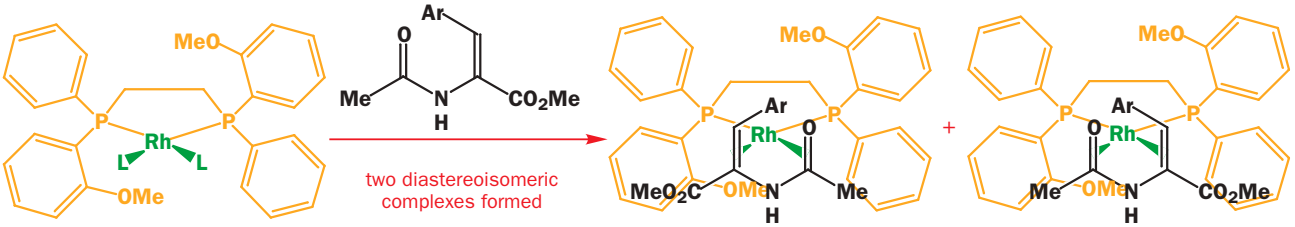


95% ee

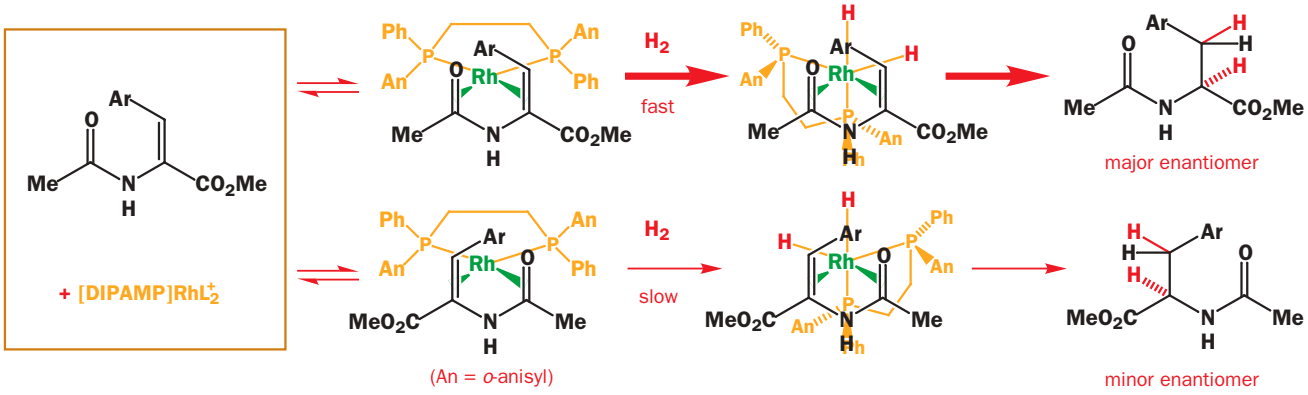
The product can be converted into L-dopa, a drug used to treat Parkinson's disease, and it is this reaction and this catalyst, both developed by Monsanto, that convinced many chemical companies that enantioselective synthesis was possible on a large scale.



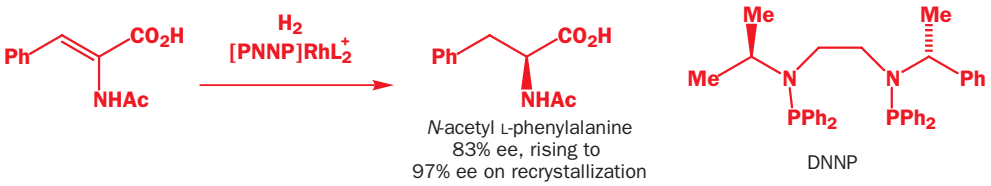
The catalyst is a cationic complex of rhodium with another diphosphine, DIPAMP. DIPAMP's chirality resides in the two stereogenic phosphorus atoms: unlike amines, phosphines are configurationally stable, rather like sulfoxides (which we will discuss in the next chapter). The catalyst imposes chirality on the hydrogenation by coordinating to both the amide group and the double bond of the substrate. Two diastereoisomeric complexes result, since the chiral catalyst can coordinate to either of the enantiotopic faces of the double bond.



It turns out that the enantioselectivity in the reaction arises because one of these diastereoisomeric complexes reacts much more rapidly with hydrogen than the other, ultimately transferring both hydrogen atoms to the same face of the double bond.



Although more limited in scope than the BINAP–Ru(II)-catalysed hydrogenations, rhodium-catalysed hydrogenations are of enormous commercial importance because of the demand for both natural and unnatural amino acids on a vast scale. It is even economical for the more expensive of the natural amino acids to be made synthetically rather than isolated from natural sources—phenylalanine, for example, of industrial importance as a component of the artificial sweetener aspartame, is manufactured by enantioselective hydrogenation.



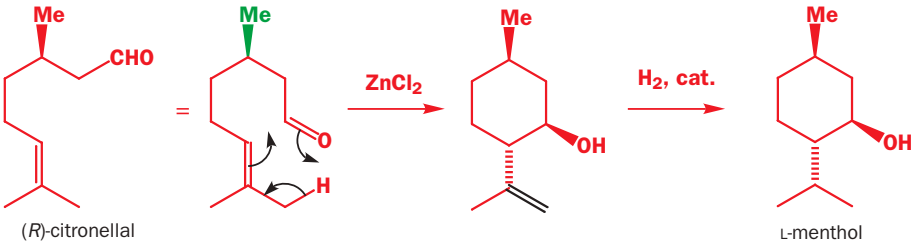
Although DIPAMP is a suitable ligand for this reaction as well, the industrial process uses the diphosphine DNNP. Unfortunately, the product is initially obtained in rather modest enantiomeric excess (83%), but recrystallization improves this to 97%. In the manufacture of aspartame,

coupling with natural (and therefore 100% ee) aspartic acid turns the 1.5% of the minor enantiomer into a diastereoisomeric impurity that can be removed by crystallization (essentially a resolution).

Improving ee by recrystallization

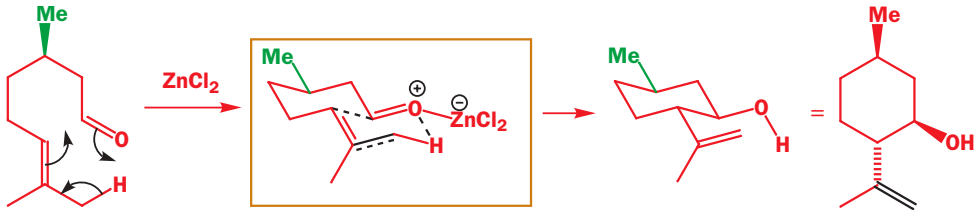
This technique is quite frequently used to improve the ee of almost enantiomerically pure samples, since, in general, crystals are most stable if they consist either of a single enantiomer or of a racemic mixture. Recrystallization of samples with ees greater than about 85% has a good chance of improving the ee of the sample (the minor enantiomer remaining in the mother liquors). Samples with ees much less than this tend to decrease in ee on recrystallization. Much depends on the crystal structure—this is quite a complex science and you can read more about it in Eliel and Wilen, *Stereochemistry of organic compounds*, Wiley, 1994. The difficulty of increasing low ees by recrystallization is one disadvantage of chiral reagent techniques as opposed to chiral auxiliary techniques.

Before leaving asymmetric hydrogenation reactions, we should mention one other related process that has acquired immense importance, again because of its industrial application. You have come across citronellol a couple of times in this chapter already: the corresponding aldehyde citronellal is even more important because it is an intermediate in the a synthesis of L-menthol by the Japanese chemical company Takasago. Takasago manufacture about 30% of the 3500 ton annual worldwide demand for L-menthol from citronellal by using an intramolecular ene reaction (a cycloaddition you met in Chapter 35).

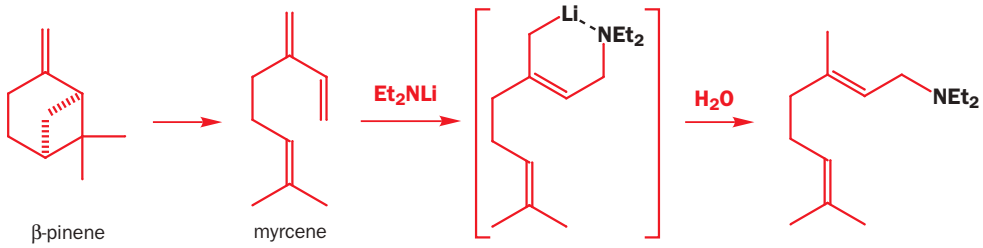


(*R*)-citronellal L-menthol

The green methyl group prefers to be equatorial in the transition state and directs the formation of the two new chiral centres. The transition state (in the frame) is like a *trans*-decalin with two fused six-membered chair rings. Both new substituents go equatorial in the product while the Lewis acid binds to the oxygen and accelerates the reaction, as it would for a Diels–Alder reaction.

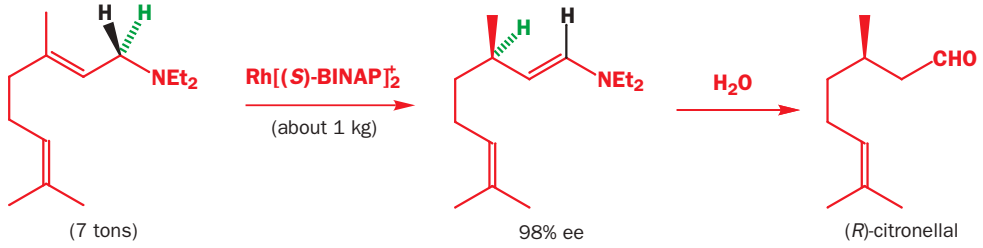


But it is not this step that makes the synthesis remarkable, but rather Takasago's route *to* citronellal. Pinene is another terpene that is produced in only low enantiomeric excess by pine trees (and, indeed, which is the major enantiomer depends on whether it is a European or a North American pine tree). But in the menthol process none of this matters, and cheap, enantiomerically impure pinene can be used, because the first step is to convert it to an achiral terpene, myrcene. Lithium diethylamide adds to this diene to give an allylic amine.



β-pinene myrcene

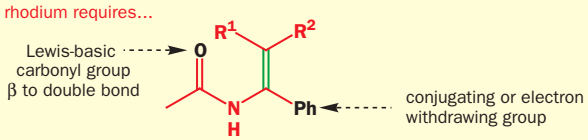
Now for the key step: $[(S)\text{-BINAP}]_2Rh^+$ catalyses the rearrangement of this allylic amine to the enamine, creating a new chiral centre with 98% ee. This reaction is rather like a hydrogenation in which the hydrogen comes from within the same molecule, or you could see it as a [1,3]-sigmatropic shift (usually disallowed) made possible by participation of the metal's orbitals. Whichever way you look at it, the catalyst selects one of two enantiotopic hydrogen atoms (shown in black and green) and allows only the green one to migrate. This reaction can be run on a seven ton scale, needs only 0.01 mol% catalyst, and is a testimony to the power of asymmetric synthesis.



Exactly how this reaction works and exactly what features of $[(S)\text{-BINAP}]_2Rh^+$ make for successful asymmetric induction are not clear. Though we can work out a mechanism for the reaction, we cannot say precisely how the chirality of the ligand directs the formation of the new stereogenic centre. Here, as elsewhere in modern organic chemistry, the experiments get ahead of human understanding.

Rhodium or ruthenium, and which ligands?

The range of diphosphine ligands used in catalytic enantioselective hydrogenation is enormous (though DIPAMP and BINAP are probably the most important), and many of them can be used with Rh or Ru. We can nonetheless give some guidelines to choice of catalyst. In general, Rh demands more of its substrates and less of its diphosphine ligands. Which ligand to choose is a matter of thorough literature searching followed by some experimentation. However, Rh will really give good ees only when hydrogenating electron-poor or conjugated double bonds that carry a β-carbonyl group (necessary for chelation), and the enamides we have been discussing are among the best of these.



Ru is more fussy about ligands (BINAP is the one usually used) but will hydrogenate both electron-rich and electron-poor double bonds. Ru[BINAP] $(OAc)_2$ works best if the double bond carries an α-hydroxyl group—in other words, if it is an allylic alcohol or an α,β-unsaturated carboxylic acid. The enantioselective hydrogenation of geraniol (p. 000) is also regioselective, because isolated double bonds are not hydrogenated.

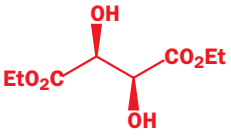
We now leave asymmetric reductions and move on to two asymmetric oxidations, which are probably the two most important asymmetric reactions known. They are both products of the laboratories of Professor Barry Sharpless.

Asymmetric epoxidation

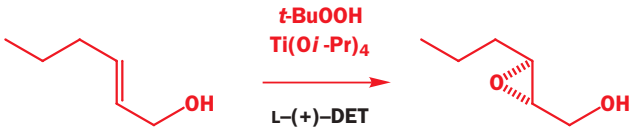
The first of Sharpless's reactions is an oxidation of alkenes by asymmetric epoxidation. You met vanadium as a transition-metal catalyst for epoxidation with *t*-butyl hydroperoxide in Chapter 33,

■ K.B. Sharpless (1941–) studied at Stanford and was first appointed at MIT but is now at the Scripps Institute in California. His undoubted claim to fame rests on the invention of no fewer than three reactions of immense significance: AE (asymmetric epoxidation) and AD (asymmetric dihydroxylation) are discussed in this chapter. The third reaction, AA (asymmetric aminohydroxylation) has still to reach the perfection of the first two.

and this new reaction makes use of titanium, as titanium tetraisopropoxide, $Ti(OiPr)_4$, to do the same thing. Sharpless surmised that, by adding a chiral ligand to the titanium catalyst, he might be able to make the reaction asymmetric. The ligand that works best is diethyl tartrate, and the reaction shown below is just one of many that demonstrate that this is a remarkably good reaction.

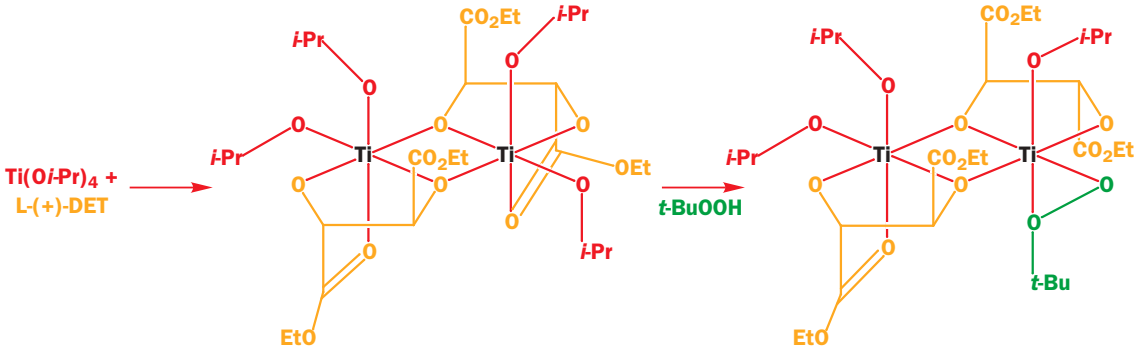


L-(+)-DET = L-(+)-diethyl tartrate



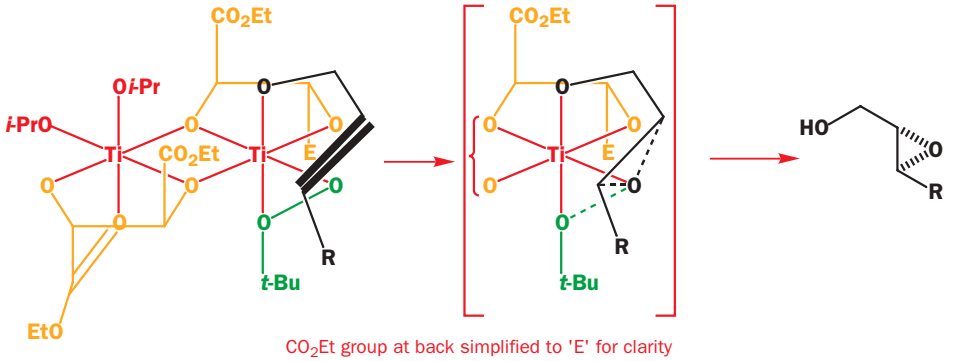
85% yield, 94% ee

Transition-metal-catalysed epoxidations work only on allylic alcohols, so there is one limitation to the method, but otherwise there are few restrictions on what can be epoxidized enantioselectively. When this reaction was discovered in 1981 it was by far the best asymmetric reaction known. Because of its importance, a lot of work went into discovering exactly how the reaction worked, and the scheme below shows what is believed to be the active complex, formed from two titanium atoms bridged by two tartrate ligands (shown in gold). Each titanium atom retains two of its isopropoxide ligands, and is coordinated to one of the carbonyl groups of the tartrate ligand. The reaction works best if the titanium and tartrate are left to stir for a while so that these dimers can form cleanly.



When the oxidizing agent (*t*-BuOOH, shown in green) is added to the mixture, it displaces one of the remaining isopropoxide ligands and one of the tartrate carbonyl groups.

Now, for this oxidizing complex to react with an allylic alcohol, the alcohol must become co-ordinated to the titanium too, displacing a further isopropoxide ligand. Because of the shape of the complex the reactive oxygen atom of the bound hydroperoxide has to be delivered to the lower face of the alkene (as drawn), and the epoxide is formed in high enantiomeric excess.

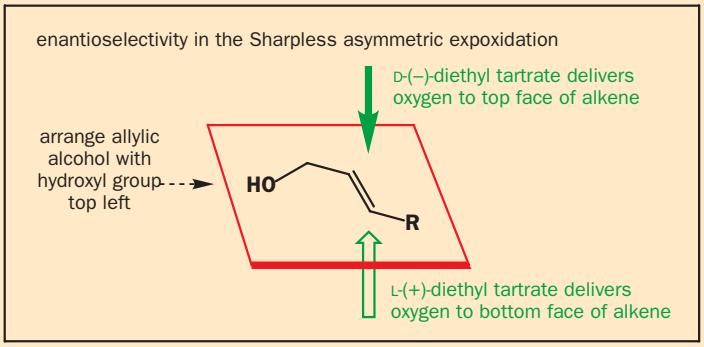


CO_2Et group at back simplified to 'E' for clarity

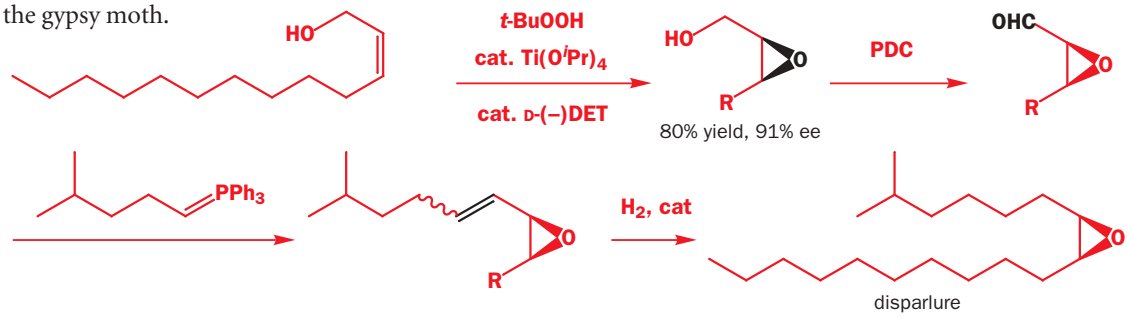
Different allylic alcohols coordinate in the same way to the titanium and reliably present the same enantiotopic face to the bound oxidizing agent, and the preference for oxidation with L-(+)-DET is shown in the schematic diagram below. Tartrate is ideal as a chiral ligand because it is available relatively cheaply as either enantiomer. L-tartrate is extracted from grapes; D-(–)-tartrate is rarer and more expensive—it is sometimes called unnatural tartrate, but, in fact, it too is natural. By using

D-(−)-tartrate it is, of course, possible to produce the other enantiomer of the epoxide equally selectively.

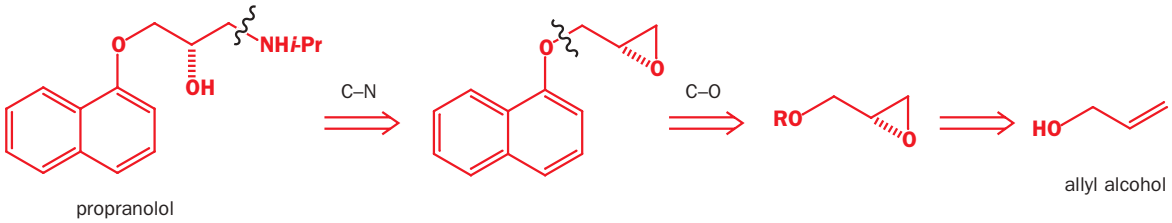
Enantioselectivity in the Sharpless asymmetric epoxidation



Sharpless also found that this reaction works with only a catalytic amount of titanium–tartrate complex, because the reaction products can be displaced from the metal centre by more of the two reagents. The catalytic version of the asymmetric epoxidation is well suited to industrial exploitation, and the American Company J. T. Baker employs it to make synthetic disparlure, the pheromone of the gypsy moth.

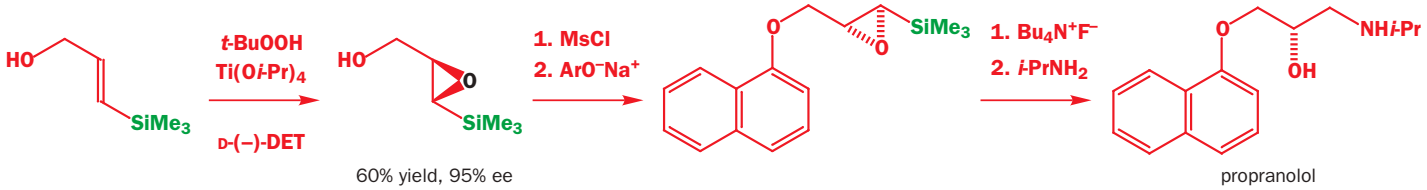


Not many target molecules are themselves epoxides, but the great thing about the epoxide products is that they are highly versatile—they react with many types of nucleophiles to give 1,2-disubstituted products. You met the chiral β-blocker drug propranolol in Chapter 30, and its 1,2,3-substitution pattern makes it a good candidate for synthesis using asymmetric epoxidation.



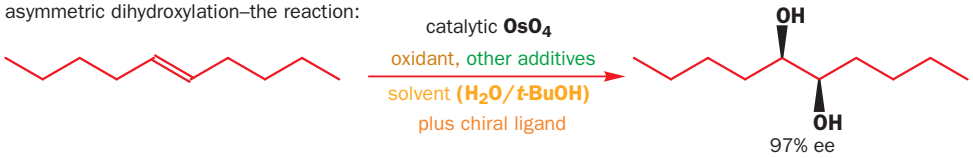
Unfortunately, the obvious starting material, allyl alcohol itself, gives and epoxide which is hard to handle, so Sharpless, who carried out this synthesis of propranolol, used this silicon-substituted allylic alcohol instead.

The hydroxyl group was mesylated and displaced with 1-naphthoxide and, after treatment with fluoride to remove the silicon, the epoxide was opened with isopropylamine.

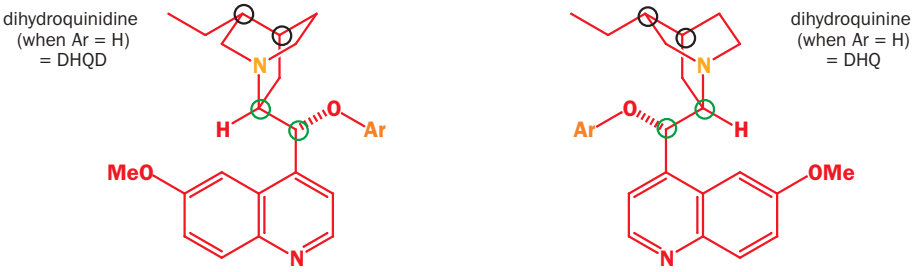


Asymmetric dihydroxylation

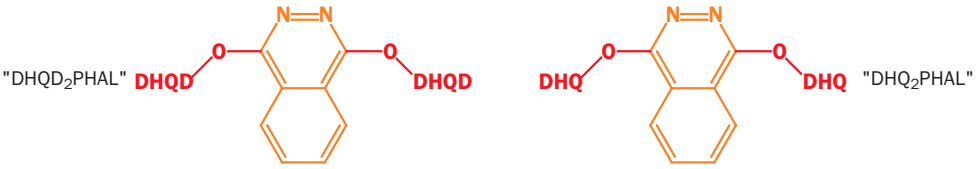
The last asymmetric oxidation we will mention really is probably the best asymmetric reaction of all. It is a chiral version of the *syn* dihydroxylation of alkenes by osmium tetroxide. Here is an example—though the concept is quite simple, the recipe for the reactions is quite complicated so we need to approach it step by step.



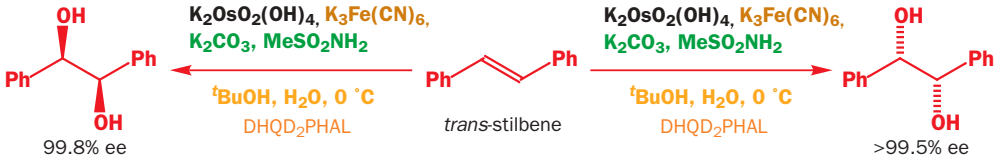
The active reagent is based on osmium(VIII) and is used in just catalytic amounts. This means that there has to be a stoichiometric quantity of another oxidant to reoxidize the osmium after each catalytic cycle—$K_3Fe(CN)_6$ is most commonly used. Because OsO_4 is volatile and toxic, the osmium is usually added as $K_2OsO_2(OH)_4$, which forms OsO_4 in the reaction mixture. The 'other additives' include K_2CO_3 and methanesulfonamide ($MeSO_2NH_2$), which increases the rate of the reaction. Now for the chiral ligand. The best ones are based on the alkaloids dihydroquinidine and dihydroquinine, whose structures are shown below. They coordinate to the osmium through the yellow nitrogen.



The alkaloids (usually abbreviated to DHQD and DHQ, respectively) must be attached to an aromatic group Ar, the choice of which (like the choice of ligand for enantioselective hydrogenation with Rh) varies according to the substrate. The most generally applicable ligands are these two phthalazines in which each aromatic group Ar carries two alkaloid ligands.

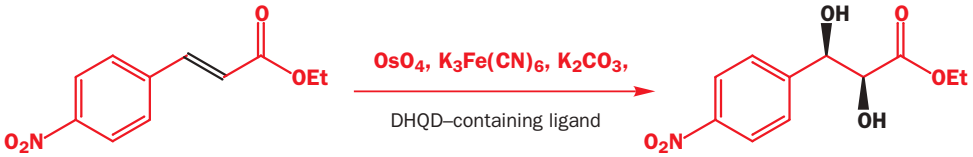


Dihydroquinine and dihydroquinidine are not enantiomeric (although the green centres are inverted in dihydroquinidine, the black ones remains the same), but they act on the dihydroxylation as though they were—here, after all that introduction, is a real example, and probably the most remarkable of any in this chapter.



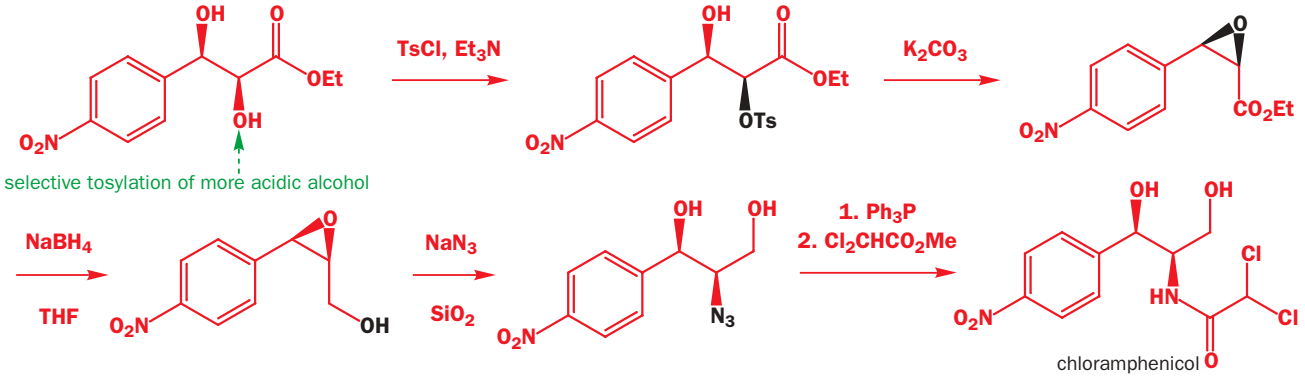
trans-(*E*)-Stilbene dihydroxylates more selectively than any other alkene, and we would probably not be exaggerating if we said that this particular example is the most enantioselective catalytic reaction ever invented. It is also much less fussy about the alkenes it will oxidize than the asymmetric epoxidation. Osmium tetroxide itself is a remarkable reagent, since it oxidizes more or less any sort of alkene, electron-rich or electron-poor, and the same is true of the asymmetric dihydroxylation

(often abbreviated to AD) reagent. The following example illustrates both this and a synthetic use for the diol product.



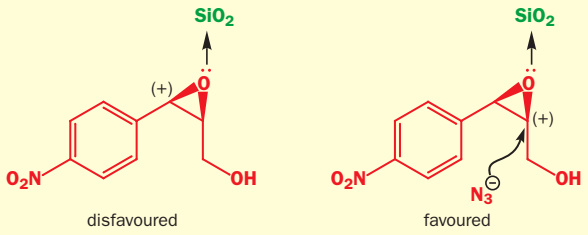
89% yield, 96% ee

The diol is produced from a double bond that is more electron-poor than most, and can be converted to the antibiotic chloramphenicol in a few more steps.



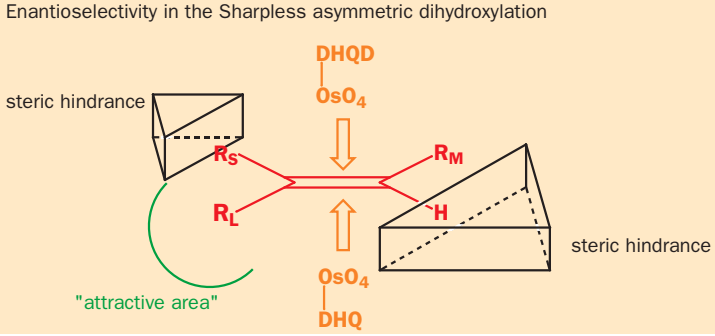
Regioselectivity in this synthesis

This sequence is not only remarkable for the AD reaction—the regioselectivites involved in the formation and reaction of the epoxide need commenting on too. The tosylation is selective because the hydroxyl group near the electron-withdrawing ester is more acidic than the other one—high selectivity here is crucial because tosylation of the other hydroxyl group would lead to the other enantiomer of the epoxide. The regioselectivity of attack of azide on the epoxide must be because of the electron-withdrawing *p*-nitro group—acidic silica encourages the reaction to proceed through an S_N1-like (or 'loose S_N2') transition state, with cationic character on the reaction centre. Substitution next to the ring is disfavoured, and the 1,3-diol is formed selectively.



We can sum up the usual selectivity of the AD reaction in another diagram, shown below. With the substrate arranged as shown, with the largest (R_L) and next largest groups (R_M) bottom left and top right, respectively, DHQD-based ligands will direct OsO_4 to dihydroxylate from the top face of the double bond and DHQ-based ligands will direct it to dihydroxylate the bottom.

Enantioselectivity in the Sharpless asymmetric dihydroxylation



The reason for this must, of course, lie in the way in which the substrate interacts with the osmium–ligand complex. However, even as we write this book, the detailed mechanism of the asymmetric dihydroxylation is still under discussion. What is known is that the ligand forms some sort of

'chiral pocket', like an enzyme active site, with the osmium sitting at the bottom of it. Alkenes can only approach the osmium if they are correctly aligned in the chiral pocket, and steric hindrance forces the alignment shown in the scheme above. The analogy with an enzyme active site goes even further, since it appears that part of the pocket is 'attractive' to aromatic or strongly hydrophobic groups. This part appears to accommodate R_L, part of the reason why the selectivity in the dihydroxylation of *trans*-stilbene is so high.

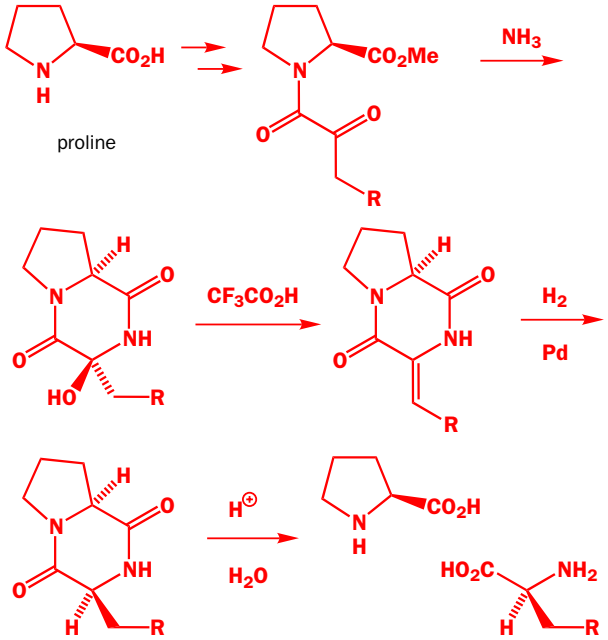
This chapter, more than most, deals with topics under active investigation. New and more powerful methods are appearing all the time and it is quite certain that the decade 2000–10 will see many important advances in asymmetric synthesis.

Summary of methods for asymmetric synthesis

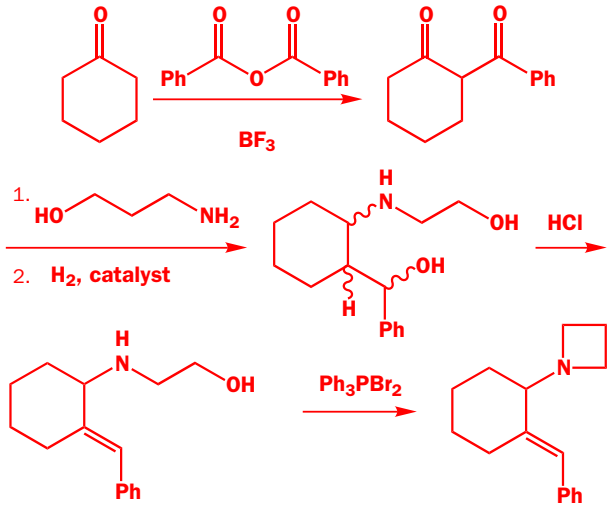
Method	Advantages	Disadvantages	Examples
resolution	both enantiomers available	maximum 50% yield	synthesis of BINAP
chiral pool	100% ee guaranteed	often only 1 enantiomer available	amino acid- and sugar-derived syntheses
chiral auxiliary	often excellent ees; can recrystallize to purify to high ee	extra steps to introduce and remove auxiliary	oxazolidinones
chiral reagent	often excellent ees; can recrystallize to purify to high ee	only a few reagents are successful and often for few substrates	enzymes, CBS reducing agent
chiral catalyst	economical: only small amounts of recyclable material used	only a few reactions are really successful; recrystallization can improve only already high ees	asymmetric hydrogenation, epoxidation, dihydroxylation

Problems

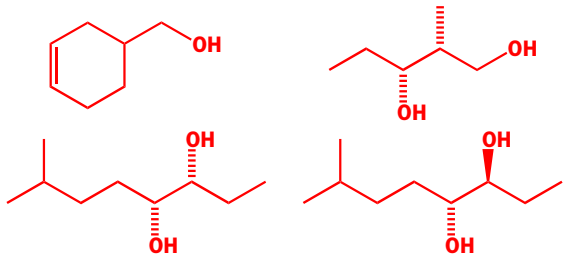
1. Explain how this asymmetric synthesis of amino acids, starting with natural proline, works. Explain the stereoselectivity of each reaction.



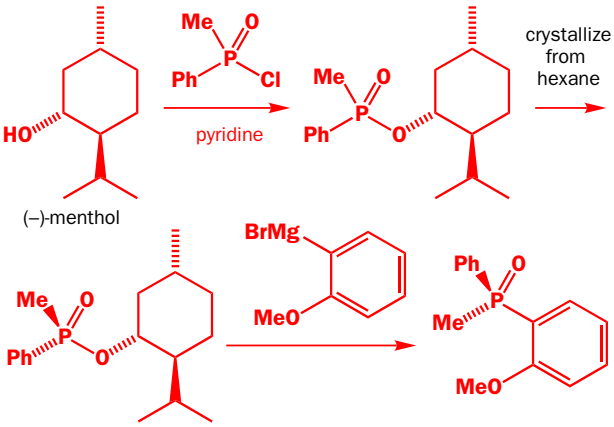
2. This is a synthesis of the racemic drug tazadolene. If the enantiomers of the drug are to be evaluated for biological activity, they must be separated. At which stage would you advocate separating the enantiomers, and how would you do it?



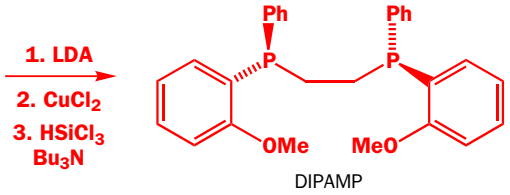
3. How would you make enantiomerically enriched samples of these compounds (either enantiomer)?



4. What is happening in stereochemical terms in this sequence of reactions? What is the other product from the crystallization from hexane? The product is one enantiomer of a phosphine oxide. If you wanted the other enantiomer, what would you do?

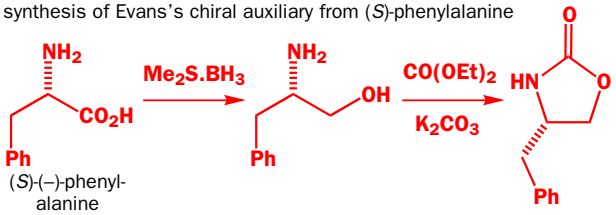


Revision. This phosphine oxide is used in the synthesis of DIPAMP, the chiral ligand for asymmetric catalytic hydrogenation mentioned in the chapter. What are the various reagents doing in the conversion into DIPAMP?

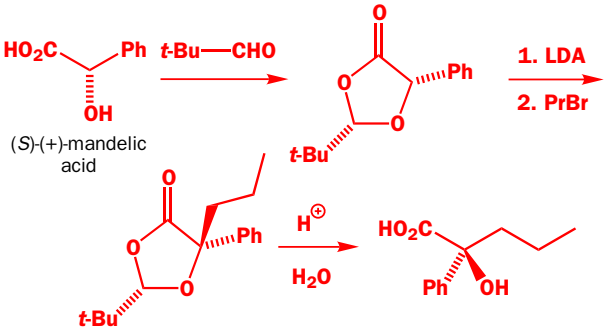


5. An alternative to the Evans chiral auxiliary described in the chapter is this oxazolidinone, made from natural (*S*)-(–)-phenylalanine. What strategy is used for this synthesis and why are the conditions and mechanism of the reactions important?

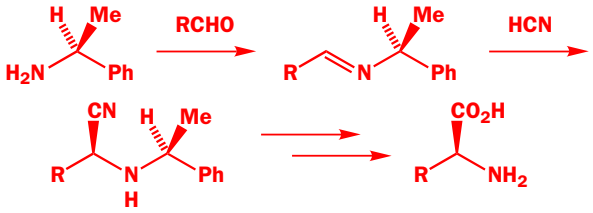
synthesis of Evans's chiral auxiliary from (*S*)-phenylalanine



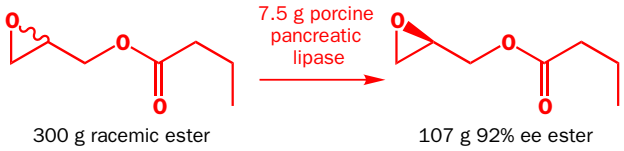
6. In the following reaction sequence, the chirality of mandelic acid is transmitted to a new hydroxy-acid by a sequence of stereochemically controlled reactions. Give mechanisms for the reactions and state whether each is stereospecific or stereoselective. Offer some rationalization for the creation of new stereogenic centres in the first and second reactions.



7. This reaction sequence can be used to make enantiomerically enriched amino acids. Which compound is the origin of the chirality and how is it made? Suggest why this particular enantiomer of the amino acid might be made. Suggest reagents for the last stages of the process. Would the enantiomerically enriched starting material be recovered?

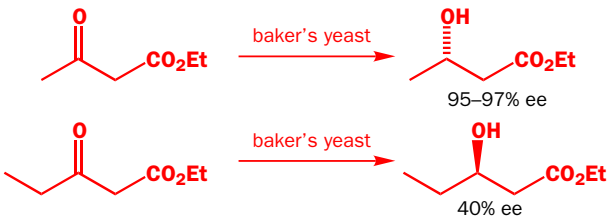


8. Submitting this racemic ester to hydrolysis by an enzyme found in pig pancreas leaves enantiomerically enriched ester with the absolute stereochemistry shown. What are the advantages and disadvantages of this method? Why is the ee not 100%?

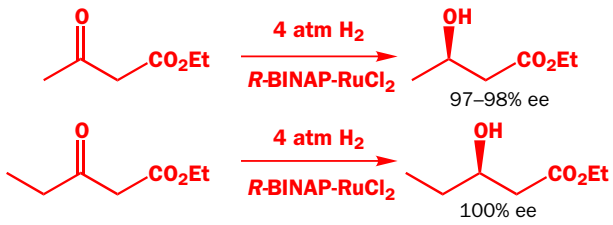


How could the same enantiomerically enriched compound be formed by chemical means? What are the advantages and disadvantages of this method?

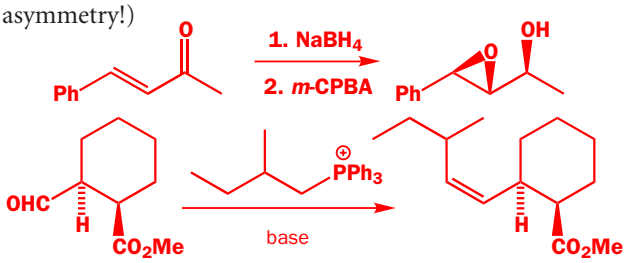
9. The BINAP-catalysed hydrogenations described in the chapter can also be applied to the reduction of ketones—the same ketones indeed as can be reduced by baker's yeast. Compare these results and comment on the differences between them.



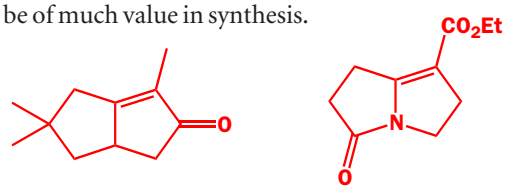
Continued overleaf



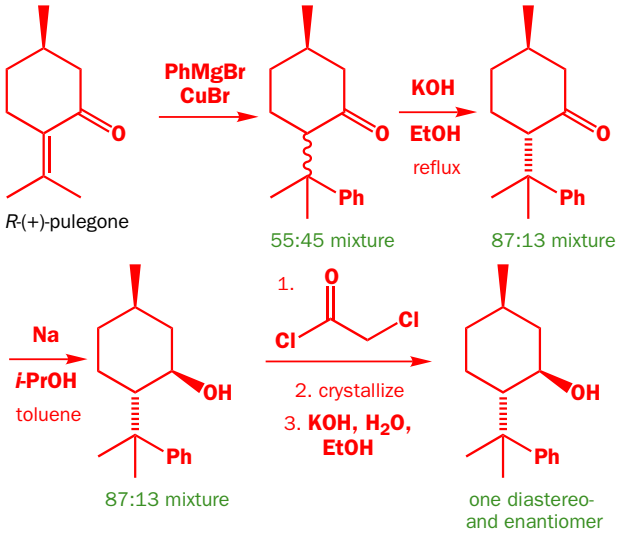
10. Describe the stereochemical happenings in these processes. You should use terms like diastereoselective and diastereotopic where needed. If you wanted to make single enantiomers of the products by these routes, at what stage would you introduce the asymmetry? (You are *not* expected to say *how* you would induce asymmetry!)



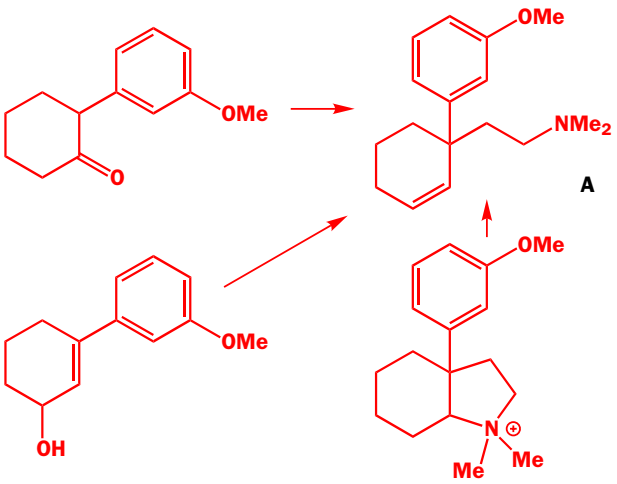
11. Both of these bicyclic compounds readily undergo hydrogenation of the alkene to give the *syn* product. Explain why asymmetric hydrogenation of only one of the compounds would be of much value in synthesis.



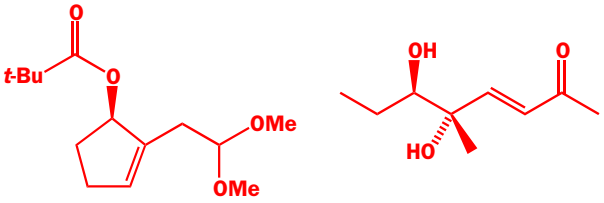
12. Explain the stereochemistry and mechanism in the synthesis of the chiral auxiliary 8-phenylmenthol from (+)-pulegone. After the reduction with Na in *i*-PrOH, what is the minor (13%) component of the mixture?



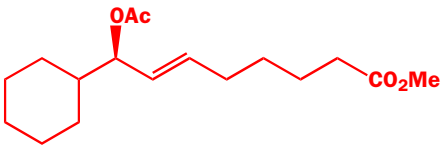
13. The unsaturated amine A, a useful intermediate in the synthesis of the *amaryllidaceae* (daffodil) alkaloids, can be made from the three starting materials shown below. What kind of chemistry is required in each case? Which is best adapted for asymmetric synthesis? Outline your chosen synthesis.



14. Suggest syntheses for single enantiomers of these compounds.



15. Suggest a synthesis of any stereoisomer (for example, *R*,*Z*) of this compound.



16. Revision. Give mechanisms for the steps in the synthesis of tazadolene in Problem 2.